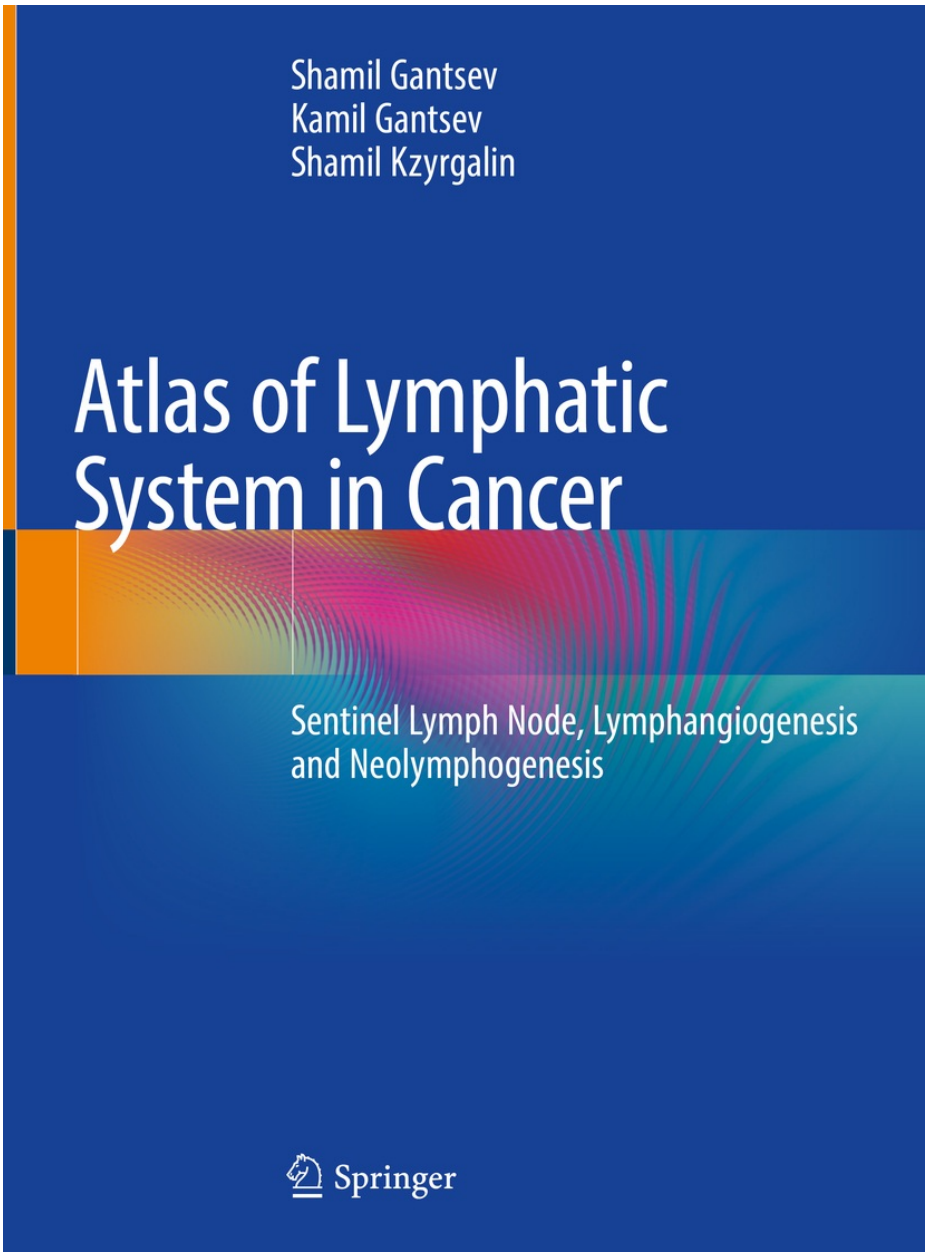
Shamil Gantsev
Kamil Gantsev
Shamil Kzyrgalin
Atlas of Lymphatic System in Cancer
Sentinel Lymph Node, Lymphangiogenesis and Neolymphogenesis
Springer

Shamil Gantsev, Kamil Gantsev and Shamil Kzyrgalin

Atlas of Lymphatic System in Cancer
Sentinel Lymph Node, Lymphangiogenesis and Neolymphogenesis

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Abstract

The study of the primary tumor has always been dominant in the planning of basic and clinical studies in oncology. In recent years, there has been a clear shift in scientific interests towards the study of the metastatic properties of cancer cells. Despite the large number of studies in the field of metastatic processes, there are many unresolved issues.

Typically, the circulatory and lymphatic systems are involved in metastasis. However, the lymphatic system is most often the primary focus of metastasis. Indeed, in many cases, the detection of tumor metastases in regional lymph nodes is the first step in the spread of the tumor, as well as one of the most important prognostic markers for the patient.

Historically, lymphatic vessels have been considered passive participants in the process of metastasis, providing only the transit of tumor cells to the lymph nodes. The discovery of several key specific lymphatic molecular markers and the increased availability of in vivo and in vitro experimental systems for the study of lymphatic function have provided a much more complex and active role in tumor metastasis.

This atlas contains a large number of original figures illustrating the anatomy, research methods, and structural features of the lymphatic apparatus in cancer. Shown are lymphatic maps of the axillary region in cancer, including those with manifestations of neolymphangiogenesis; newly formed lymph nodes formed as a result of neolymphogenesis.

It is intended for oncologists, surgeons, anatomists, morphologists, and doctors of other specialties. It is the result of 10 years of research. The applied technology of ultrasonic isolation of anatomical structures made it possible to take a fresh look at the lymphatic apparatus in cancer and to discover the previously not described phenomenon of neolymphogenesis. We

hope that this publication will help advance in understanding the logistics of metastasis.

Reviews

The publication,*Atlas of Lymphatic System in Cancer: Sentinel Lymph Node, Lymphangiogenesis, and Neolymphogenesis* , by Shamil Gantsev, Kamil Gantsev, and Shamil Kzyrgalin represents a generously illustrated catalogue of the role of the lymphatic system in cancer metastasis. I consider this work novel and clinically relevant for understanding the complex processes involved in tumor cell spread through the lymphatic system. The authors describe the change from considering the lymphatic vessels and the lymph nodes as “passive structures” in the transit of spreading tumor cells to a complex system which actually plays an “active role” in the process of tumor metastasis. The atlas contains seven well-written and well-illustrated chapters (including introduction and conclusion); among those chapters, novel and clinically important aspects are particularly discussed in Chapter 2 (“Lymph Nodes in Cancer: Sentinel Lymph Node”) and Chapter 5 (“Neolymphogenesis”). As – to my opinion – there

is no comparable work so far in the published literature, I highly recommend this publication. The insights from this work will help promote further research – both morphologically and on the molecular level – to better understand the meaning and processes in tumor cell spread through the lymphatic system.

Professor Christopher Poremba
Director, Institute of Pathology Munich, Nord
Institute of Molecular Pathology Bavaria South
Munich, Germany

The role of the lymphatic system in the development of human pathological conditions is of great importance, especially in case of tumor pathology. Therefore, this atlas is extremely popular and relevant. At present, such publications are extremely scarce and practically nonexistent. As for relevance, I can note that it is the authors of the atlas who first described the phenomenon of neolymphogenesis in the world and presented original photographs of the phenomenon of neolymphangiogenesis, experimental neolymphogenesis. It is also necessary to pay

attention to the demonstration of lymphatic maps. This is an extremely important area in oncology, providing an assessment of predicate factors.

It should be noted that all the drawings are of an original character, made on fresh postoperative anatomical preparations of the mammary gland and regional lymphatic collector.

The text of the atlas reflects the personal idea of the authors on the issue under consideration. The atlas is written in English and is intended for distribution in leading libraries in the world (the USA, Canada, England, China, Japan, Australia, etc.). The English language was edited by a native English speaker from Oxford (England).

I believe that the atlas edited by Professor Gantsev, scheduled for publication, will serve the cause of the development of fundamental and clinical medicine.

Professor V.M. Timerbulatov,

Corresponding Member, Russian Academy of Sciences

President, Association of Surgeons of the Republic of Bashkortostan

Ufa, Republic of Bashkortostan, Russian Federation

The lymphatic system is essential for the proper functioning of an organism. As an anatomical correlate of a part of the immune system, the reticuloendothelial system contributes significantly to the protection as well as to the detoxification of the body. Since the discovery of the lymphatic system by Italian field surgeon Gaspard Aselli (1622) and Danish anatomist Thomas Bartholin (1653) there was a significant growth in understanding that lymphatic system plays an active part in the defence of the organism, its immune and antitumor role. The morphological studies presented here by Gantsev et al. show, very nicely, that lymphatic vessels and the lymph nodes are not just static system, but they adapt perfectly to the respective requirements.

Using the methods of modern anatomy, the authors show this change in their atlas at both the macroscopic and the microscopic levels. The architectonics is important in the issues of lymphatic system surgery, including the navigation of sentinel lymph node search and organ-preserving treatment.

Professor Gerhard Schaller
Head of Breast Care Institute
Munich, Germany

Angiogenesis (blood vessel formation) and lymphangiogenesis (lymphatic formation) are important processes for the organization and maintenance of most tissues in the physiological state. In the pathological state, they are also important for the regulation of inflammation and cancer.

Angiogenesis has been extensively studied, and its methodology for research has been well developed. Many growth factors have been reported for angiogenesis, and its clinical importance is well known. Yet, lymphangiogenesis has still been poorly understood in its methodology, mechanism, and clinical importance.

This atlas, written by Professor Shamil Gantsev and co-authors of, Bashkir State Medical University, Ufa, shows many engaging lymphatic preparations and unique methods, especially in breast cancer, and should be useful for further basic and clinical studies on lymphatics.

Excess angiogenesis and cancer-specific angiogenesis often accelerate tumor growth. So we try to inhibit cancer angiogenesis using molecular target medicine such as anti-VEGF antibody or VEGF signal inhibitors. Meanwhile, the role of lymphatics in cancer has not been fully understood. Prof. Gantsev proposes lymphatic formation may inhibit cancer growth from his clinical studies. This is a unique and attractive idea.

On the whole, this atlas on lymphology is very original and interesting to read. It provides pictures of lymphatics very clearly. I would like to recommend this book to biologists and clinicians in the field of cancer an inflammation.

Professor Kazuo Umezawa
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Introduction

Cancer has gained the signs of an epidemic. Annually, all over the world, millions of people get sick with this disease. With increasing life expectancy, the number of patients increases annually. At the same time, over the past decades, trends in the increase of hormone-dependent neoplasms have been identified everywhere, among which breast cancer dominates. Mortality rates are also of particular concern.

In our opinion, to date, the world's oncology has reached a certain point, when there are real prerequisites for a breakthrough in understanding intimate issues of cancer nature, conceptual mechanisms of carcinogenesis. This breakthrough may be in interaction with tumor and its carrier, biological cluster responsible for carcinogenesis, and the entire biological system of the body as a whole.

The study of primary tumor was always dominant in planning of fundamental and clinical research in oncology. In recent years, there has been a clear shift in research interests towards the study of metastatic properties of cancer cell. Despite a large number of studies in the field of metastasis processes, there are many unresolved issues.

As a rule, the circulatory and lymphatic systems are involved in metastasis. However, the lymphatic system is more often the initial focus of metastases. Indeed, in many cases, the discovery of tumor metastases in regional lymph nodes is the first step in tumor spread, as well as one of the most important predictive markers for a patient.

More than 100 years ago, the doctrine of cancer dissemination and the role of the lymphatic system in this complex process were formulated. But lymphology, like all other sciences, developed under the influence of new ideas. Setting updated tasks, it applied more advanced technology towards their solution and achieved

remarkable scientific results. Many scientists are studying its nature. A great contribution to the detailing and study of this problem was made by the schools of morphologists in Europe, the USA, Japan, and Southeast Asia.

Historically, lymphatic vessels have been considered to be passive participants in the process of metastasis, providing only transit of tumor cells to the lymph nodes. The discovery of several key specific lymphatic molecular markers and an increase in the availability of in vivo and in vitro experimental systems for the study of lymphatic function have provided a much more complex, active role in metastasis of tumors.

This publication contains a large number of original photographs illustrating anatomy, research methods, and peculiarities of the lymphatic apparatus structure in oncology diseases. Tissue complexes of the axillary region were studied in detail. New data on lymphangiogenesis in cancer and neolymphogenesis of metastases to lymph nodes necessitate in-depth study of the possibilities of modern bioengineering in oncology and many other things.

For reader's better understanding of the presented data, it is necessary to provide additional information reflecting the meaning of some terms used in this publication. In particular, this concerns "sentinel lymph node" and "neolymphogenesis."

It is generally believed that the sentinel lymph node is the first node receiving lymph from the tumor, potentially containing metastatic cells. Within our practical activity, we consider the sentinel lymph node to be the node with the most active lymphangiogenesis. That is, from our point of view, not the proximity of the node to the tumor determines its role in the dissemination of tumor cells but its functional activity.

There is another issue that is of great interest for clinicians, namely, the quantity of sentinel lymph nodes. Earlier, we agreed with the opinion of our colleagues that these nodes could be

several. In this publication, we want to note that, one way or another, the sentinel lymph node can be represented in singular at a specific point of time scale. But if during metastatic disease one sentinel lymph node loses its superiority regarding lymphangiogenesis intensity, the sentinel one becomes a node having more active lymphangiogenesis. It is important to note that these nodes can adhere, forming conglomerates, and also can be disposed in a disconnected manner. We were prompted to this interpretation by our observations, when, according to the classical definition of the sentinel lymph node, the first lymph node taking the outflow from tumor region was free from metastatic lesion, while being in afunctional state due to the total intracapsular replacement with adipose tissue, the second-order lymph node had a metastatic lesion and active lymphangiogenesis. Summarizing this situation, it can be stated that during pathological process, there can be several sentinel lymph nodes: if the first lymph node ceases to perform its functions, the first duplicating node becomes active, then the second duplicating node, etc. Therefore, this is a constant process: one node functionally replaces another one.

Neolymphogenesis – the formation of lymphoid aggregates – is a phenomenon of the special structural organization of peripheral lymphoid tissue. The formation of ectopic (tertiary) lymphoid structures is observed in infections and autoimmune as well as oncology diseases. The newly formed lymphoid tissue can be both simple lymphocyte aggregates and highly organized formations, characteristics for complete lymph nodes.

We described the phenomenon of neolymphogenesis in cancer in 2009. In the context of this publication, “neolymphogenesis” is the formation of new lymph nodes of a simplified structure, observed with loss of the functions of regional lymph nodes and, first of all, a first-order sentinel lymph node.

The pathogenetic and clinical relevance of such structures’

formation in oncology diseases and chronic inflammatory processes is not clear for the moment. The results of some studies demonstrate the protective effect of this phenomenon; in others, the authors emphasize its connection with the adverse disease outcome. In our point of view, neolymphogenesis in cancer is an example of activation of adaptive resources and self-regulation of biological systems in the development of neoplastic process. The development of newly formed lymph nodes in cancer can be considered as a compensatory mechanism of natural antitumor protection.

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5 Neolymphogenesis

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1. Methods of Lymphatic Dissection

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Keywords Lymphatic system – Axillary lymphatic apparatus – Breast cancer – Materials and methods – Dissection – Sonolipodestruction – Ex vivo lymphography

Mobilization of organs, tissues, and other formations is the most important component of research activity in anatomy and pathology. The lymphatic system is of particular interest, its components are surrounded by fatty tissue, and their routine dissection is very difficult. The study of the lymphatic apparatus is an extremely important diagnostic step in oncology clinic, and possibly, it is also a leading step for prognosis and paradigm of personalized treatment. Nowadays, oncologists and surgeons use several types of lymphatic dissection (by volume):

1. “Blind” instrumental dissection. It is performed with surgical

instruments. All lymph nodes of a specific basin are removed with adipose tissue [(base) (B)] according to their localization, without going into details (B +).

2. “Visual” instrumental dissection. It is performed with surgical instruments. In this type of dissection, the largest lymph node is first isolated, and then, other nodes are successively dissected from it, and the fat mass (B−) is not touched.

Other techniques are used in ex vivo dissections:

1. “Visual” instrumental dissection with surgical instruments (B−).
2. Chemical lipolysis. This technique allows you to save all the main components of regional lymphatic apparatus, without significant morphological and traumatic damage to the tissues (B 0).
3. Ultrasonic lymphatic dissection. When using ultrasound, it is achieved the maximum effect of adipose tissue removal, without damaging stromal components, lymphatic drainage system, and lymph nodes (B 0). This technique can be considered as the “gold” standard of lymphatic dissection in oncology diseases for cancer staging according to the N ex vivo criterion and scientific research.

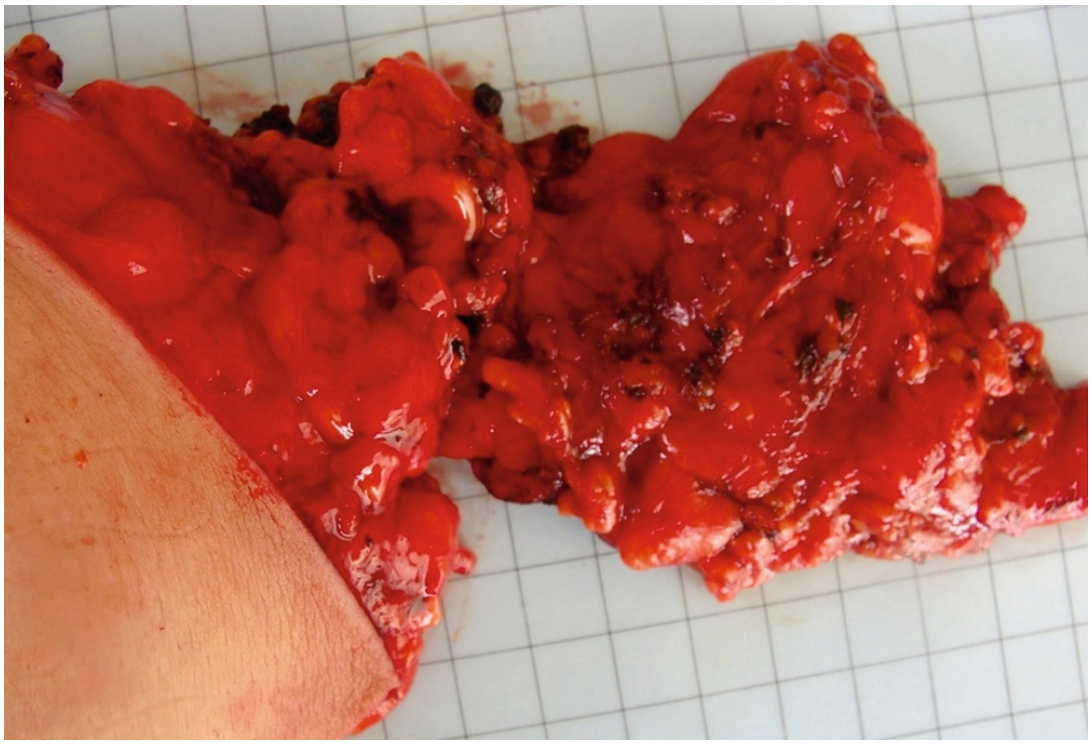

Fig. 1.1 Gross specimen of mammary gland with axillary fiber prepared for lymphatic dissection (dissection volume B+)

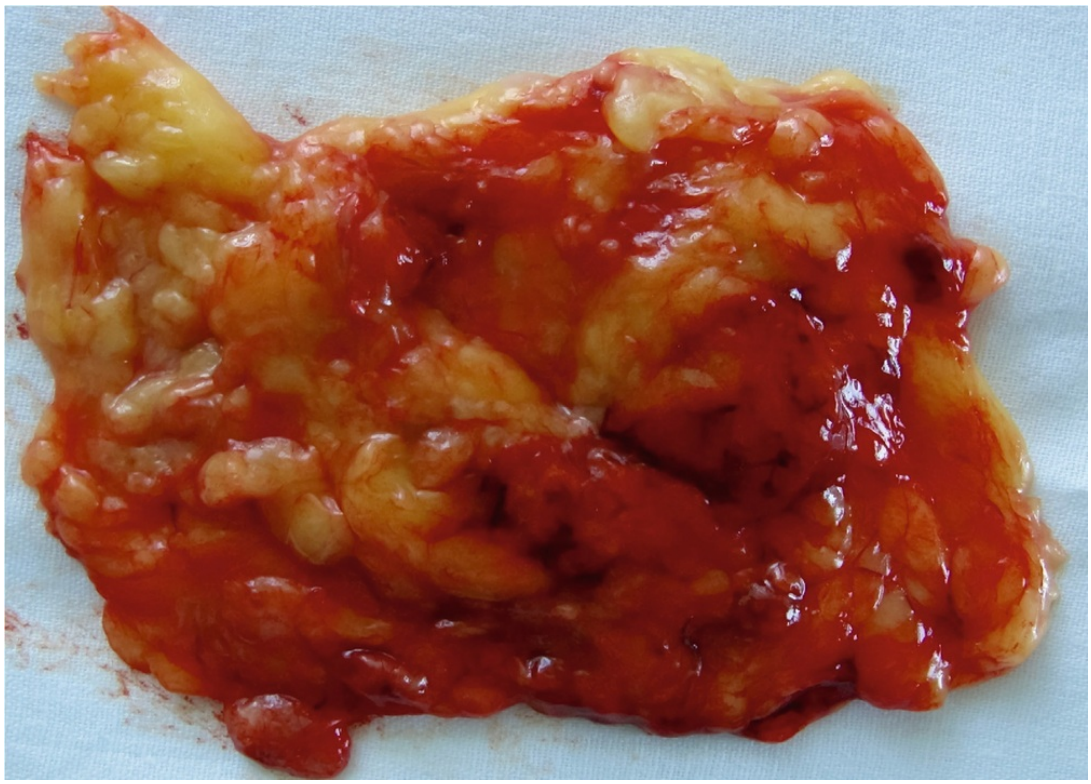

Fig. 1.2 Axillary adipose tissue prepared for lymphatic mapping isolation by dissection

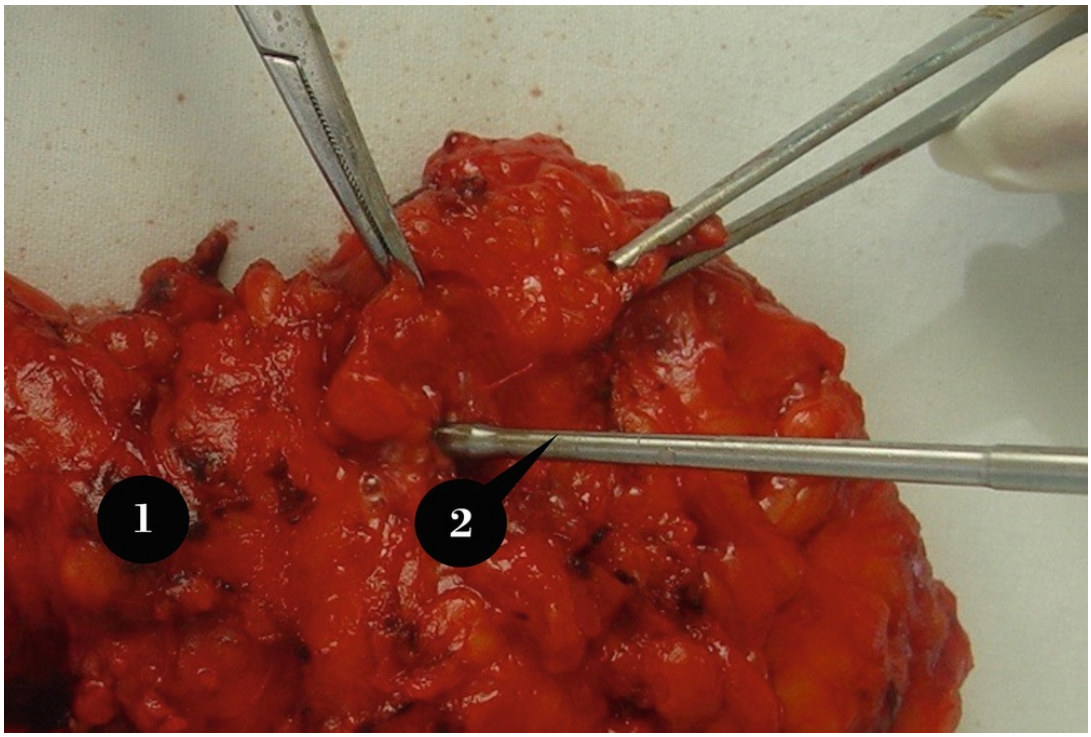

Fig. 1.3 The ultrasonic technology is used for dissection of ultrathin anatomical structures; it allows to open access to the lymph nodes and their surroundings by fat cavitation. The use of this method allows preserving microcirculation vessels without significant damage to their structure. The figure illustrates the initial stage of ex vivo surgery for isolation of stroma and its components in the axillary region in breast cancer with metastases: 1 adipose tissue of the axillary region and 2 an applied part (catheter) of ultrasonic dissector

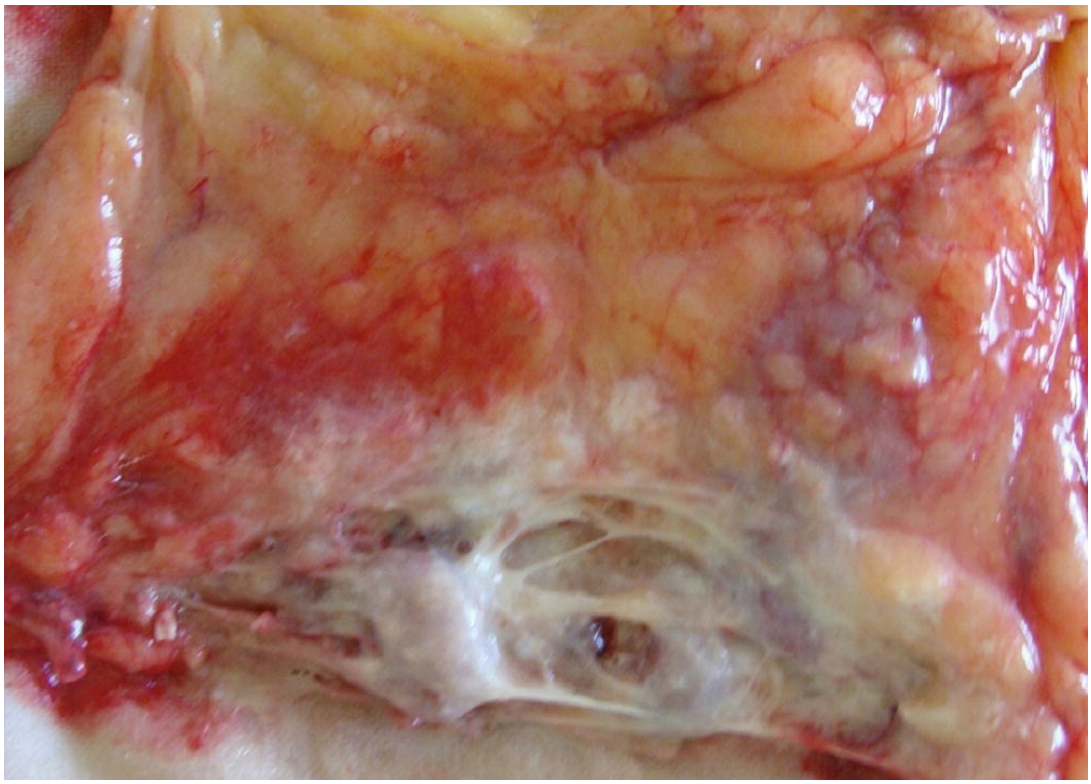

Fig. 1.4 The fragment of adipose tissue of the axillary region. Isolation of lymph nodes is difficult due to a cicatricial affection. Prior to surgery, a patient undergone an axillary radiotherapy, which was the reason for tissue change

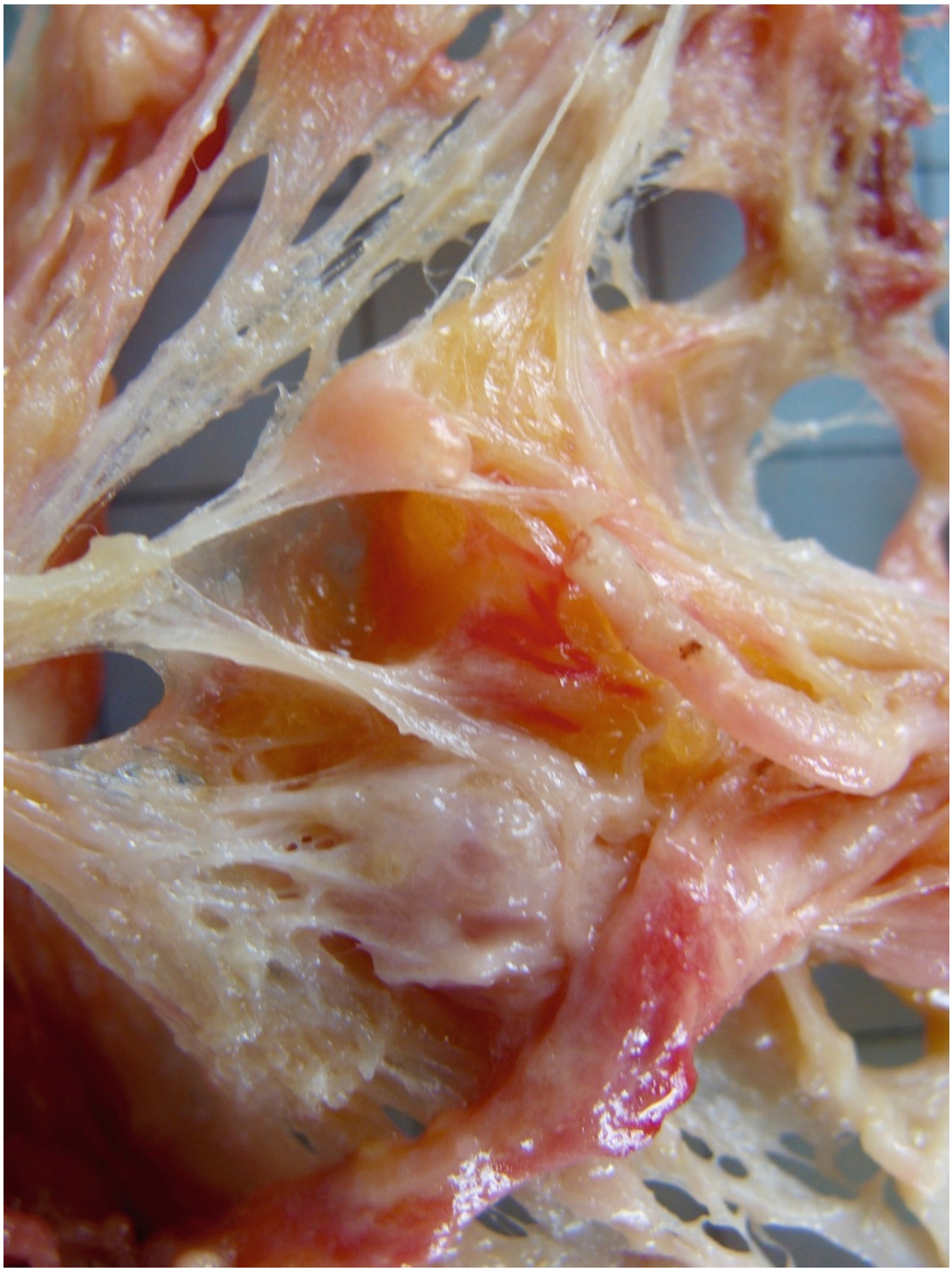

Fig. 1.5 Stroma – expressed gross specimen of the lymphatic apparatus after ultrasonic dissection. Lymph nodes are surrounded by connective tissue and a variety of vessels (dissection volume B0)

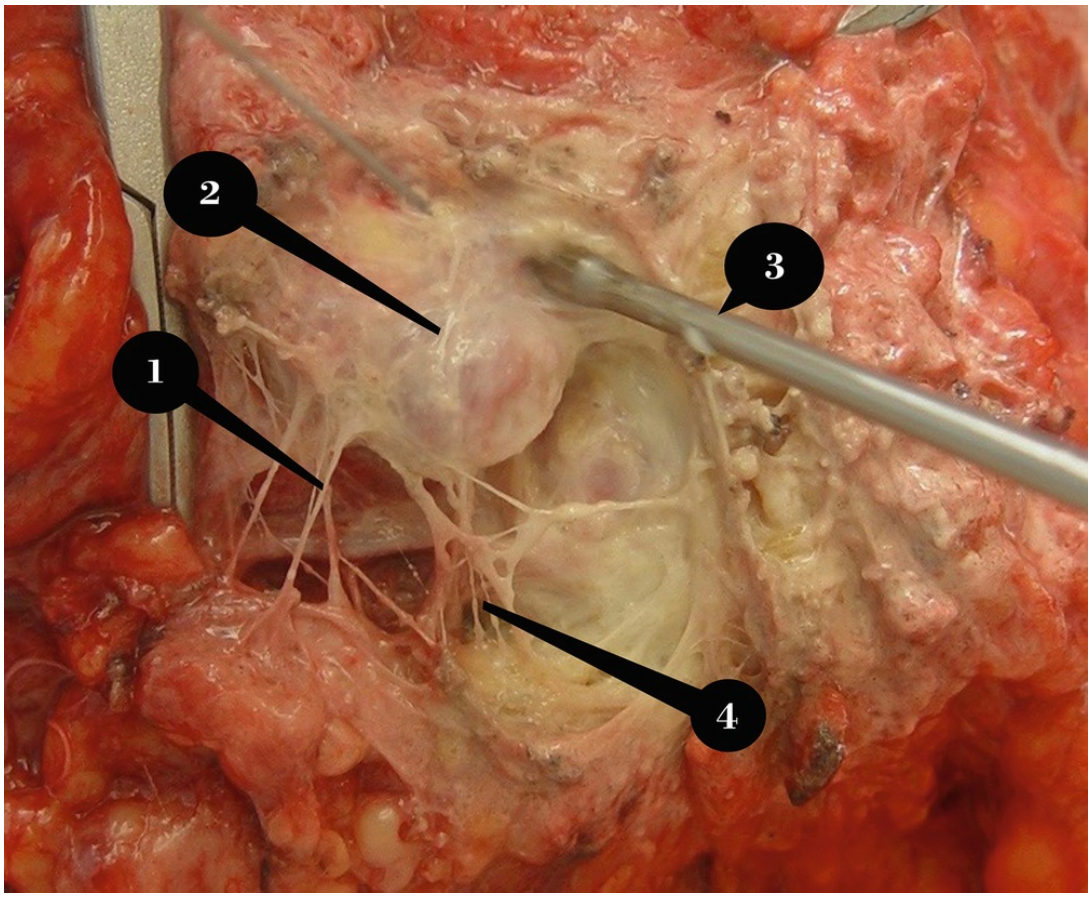

Fig. 1.6 The lymphatic dissection requires an increased attention and caution in order to avoid disruption of ultrathin vessels. The figure illustrates the main stage of ex vivo isolation of the sentinel lymph node: 1 multiple newly formed lymphatic vessels, 2 enlarged lymph node with an unchanged capsule, 3 an applied part of ultrasonic dissector, and 4 newly formed lymphatic vessels located between two lymph nodes (dissection volume B0)

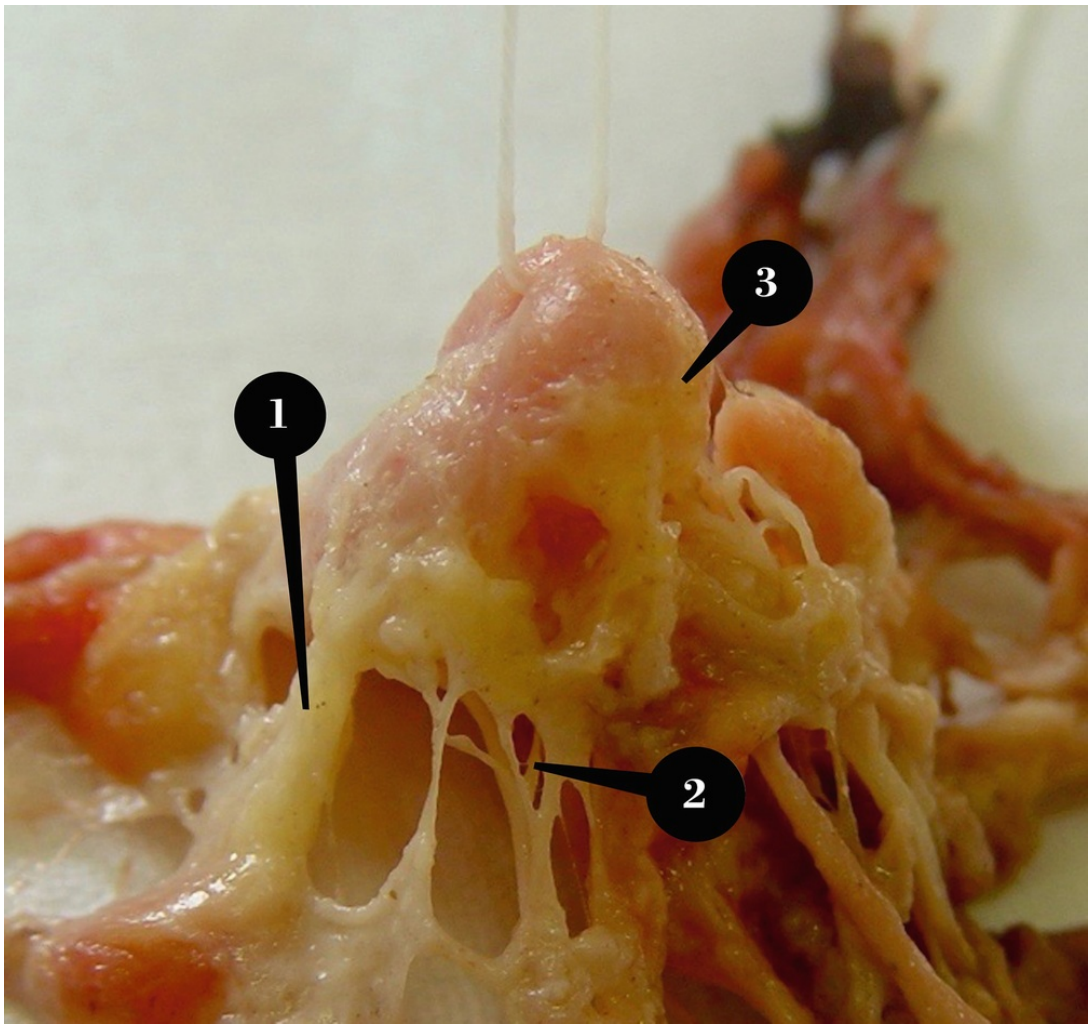

Fig. 1.7 When the lymph node is isolated by ultrasound, it is used the method of throughout suturing and traction; it makes it possible to identify all inflow and efferent vessels, filaments, and other anatomical structures in all areas. Figure 1 illustrates a large vessel (artery), 2 mature efferent lymph vessels anastomosing with each other, and 3 enlarged lymph node, bean-shaped, with fat transformation. It is observed the zone of capsule retraction, which is typical for the metastatic lesion of the lymph node segment (dissection volume B0)

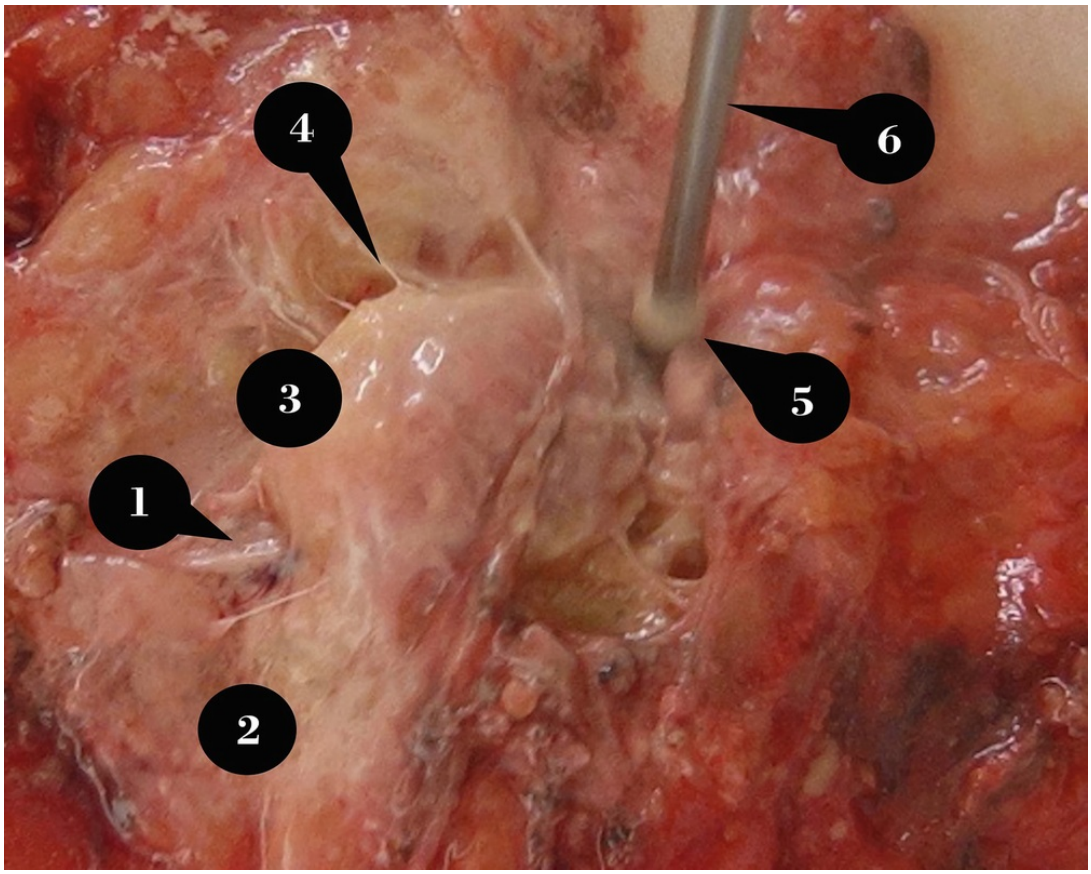

Fig. 1.8 In cancer with metastases in the axillary region, the lymph nodes form conglomerations, so dissection stage can be accompanied by destruction of nodes and vascular disruption. The figure illustrates the main allocation stage of lymph node conglomeration: 2, 3 – lymph node affected by metastases and deformed by a constriction at the hilus; it creates the illusion of two nodes' adherence. 1 – blood vessel of the lymph node hilus. The lymph nodes are connected between each other by newly formed lymphatic vessels of ultrathin size (4). 5 – melted fat forms a ring on the end part of the catheter. 6 – an applied part of ultrasonic dissector

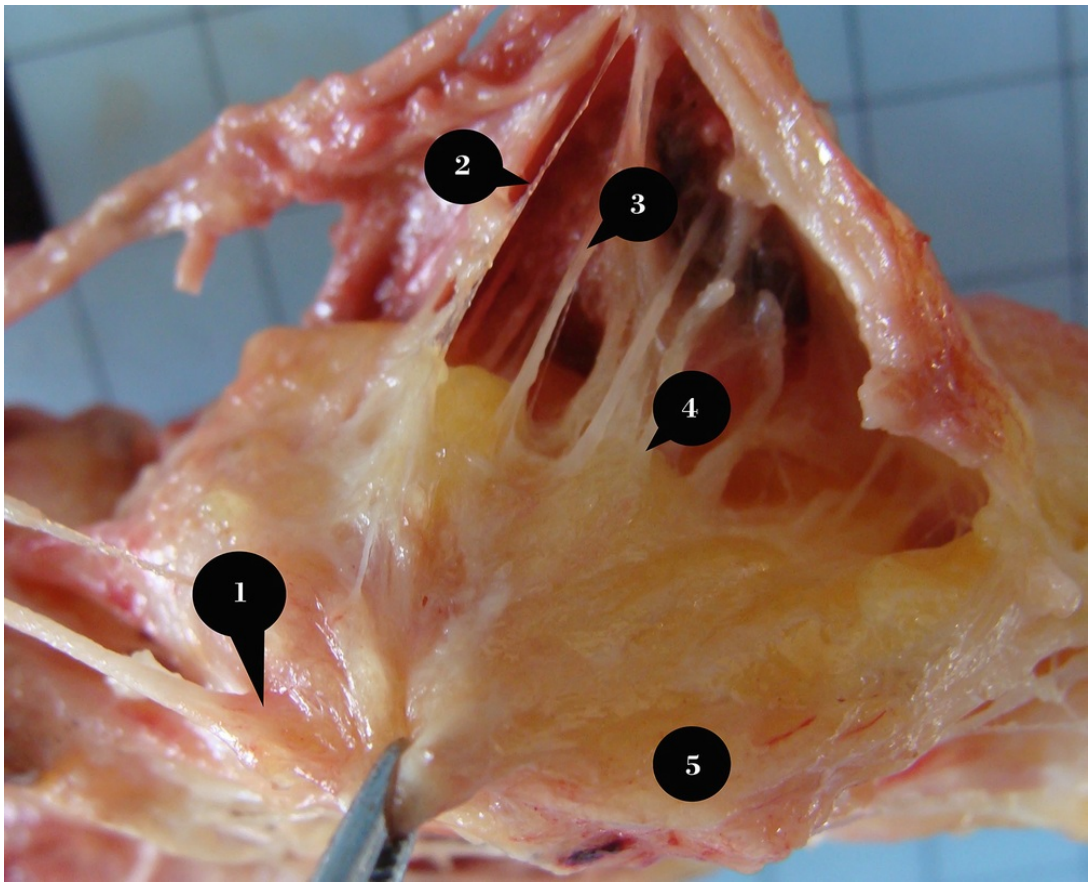

Fig. 1.9 When dissecting the lymph nodes, it is principally important to use the node traction; this technique will allow more technically identifying the vessels and determining the logistics of metastatic cell movement in the lymphatic bed. Figure 1 illustrates lymphonodular transition with a noticeable extension to the capsule surface; 2 newly formed lymphatic vessel of ultrathin structure; 3 newly formed mature lymphatic vessel; 4 native lymphatic vessel; 5 lymph node involved in the active transfer of cancer cells, as evidenced by neo-lymphangiogenesis

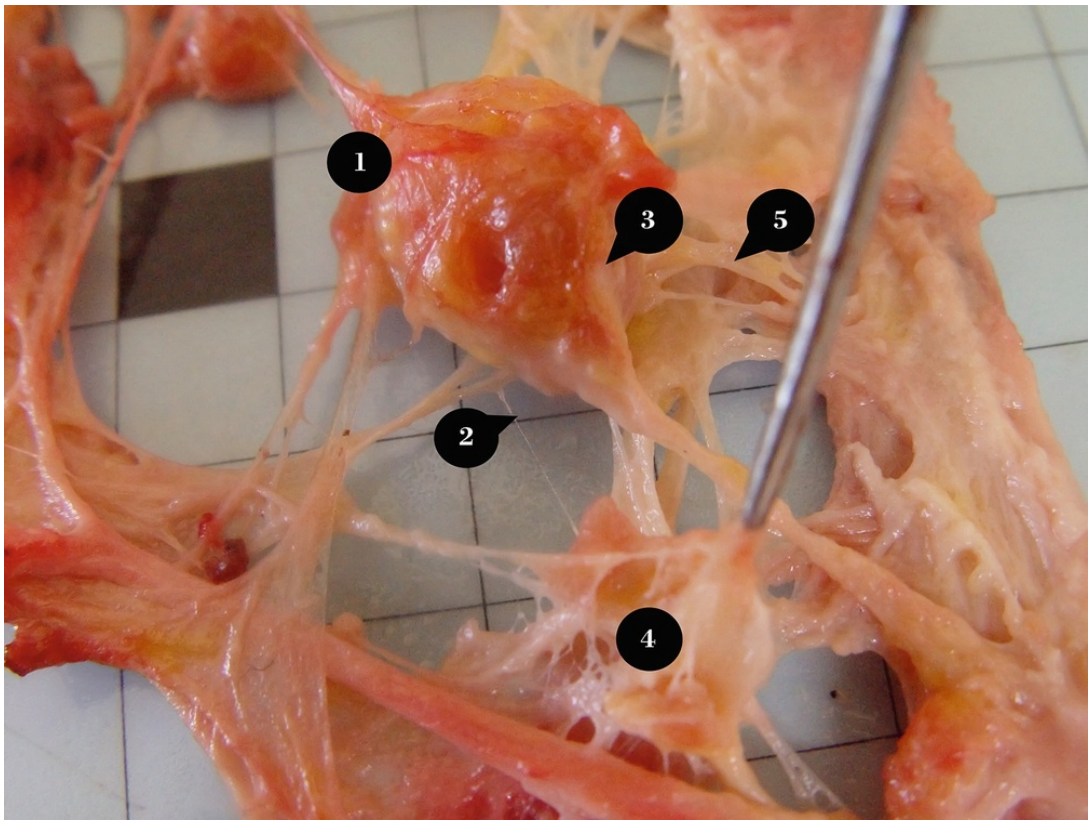

Fig. 1.10 The (1) identified lymph node is surrounded by vessels with moderate density (2,3,4,5). There is an umbilication in the center of the lymph node (widely met)

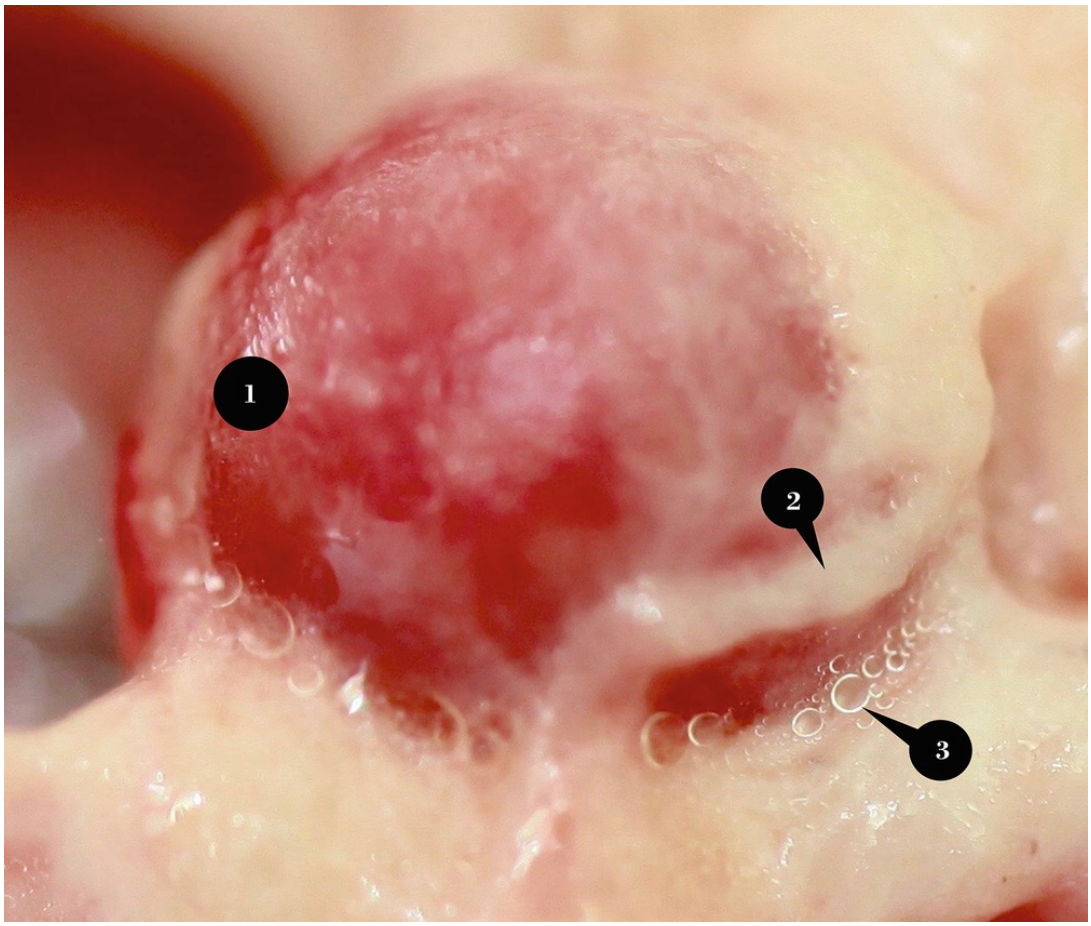

Fig. 1.11 Multiply enlarged lymph node (1). The lymph node capsule is hyperemic; it indicates its involvement in pathological process. (2) Lymphatic vessel passes around the node above the capsule and then flows to fatty tissue. In surgical area, there are fat droplets (3), visible after ultrasound treatment

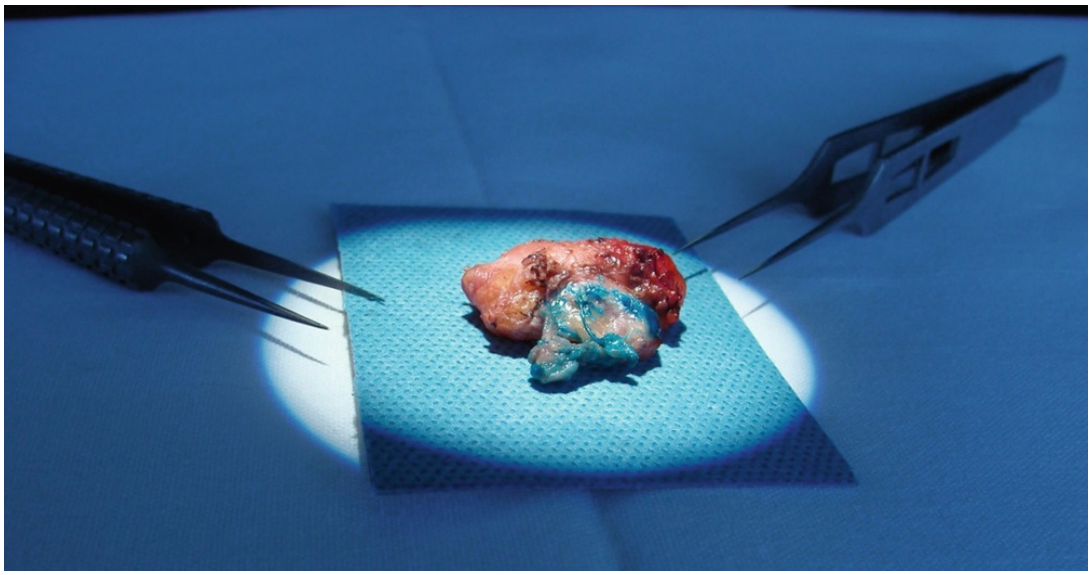

Fig. 1.12 Biomaterial is prepared for microsurgical dissection

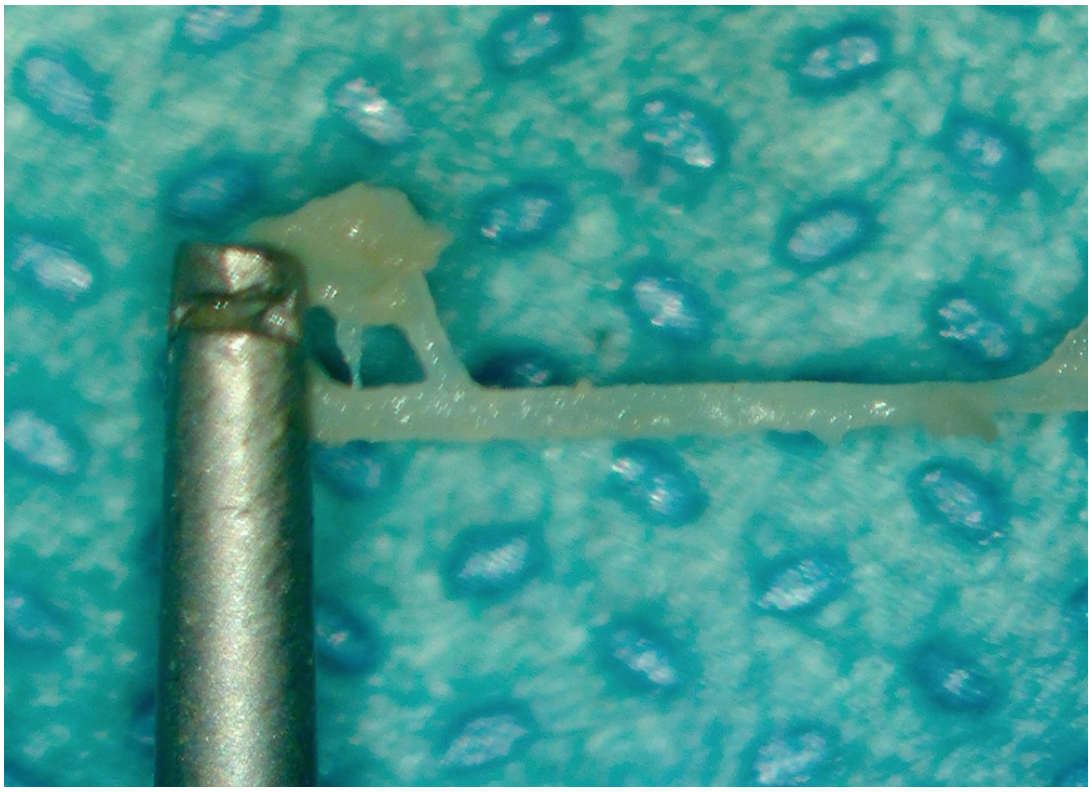

Fig. 1.13 The great lymphatic vessel is stretched using surgical forceps; the vessel is cylinder-shaped. At the place of vessel fixation with forceps, one can see the transposition of a smaller diameter lymphatic vessel

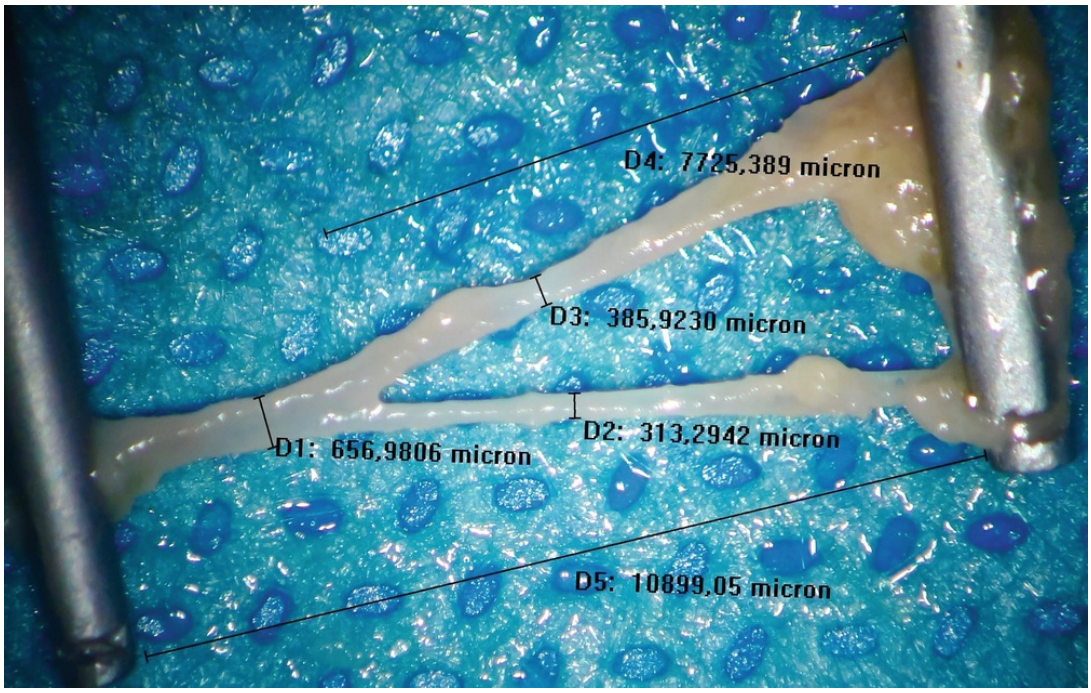

Fig. 1.14 The fragment of lymphatic vessel: morphometric data. The figure illustrates the total length of the vessel – 10.8 mm; lymphatic vessels are separated from the capsule at a level of 7.7 mm. The diameter of inflow vessels is 0.38 and 0.31 mm. The diameter of the great vessel is 0.65 mm

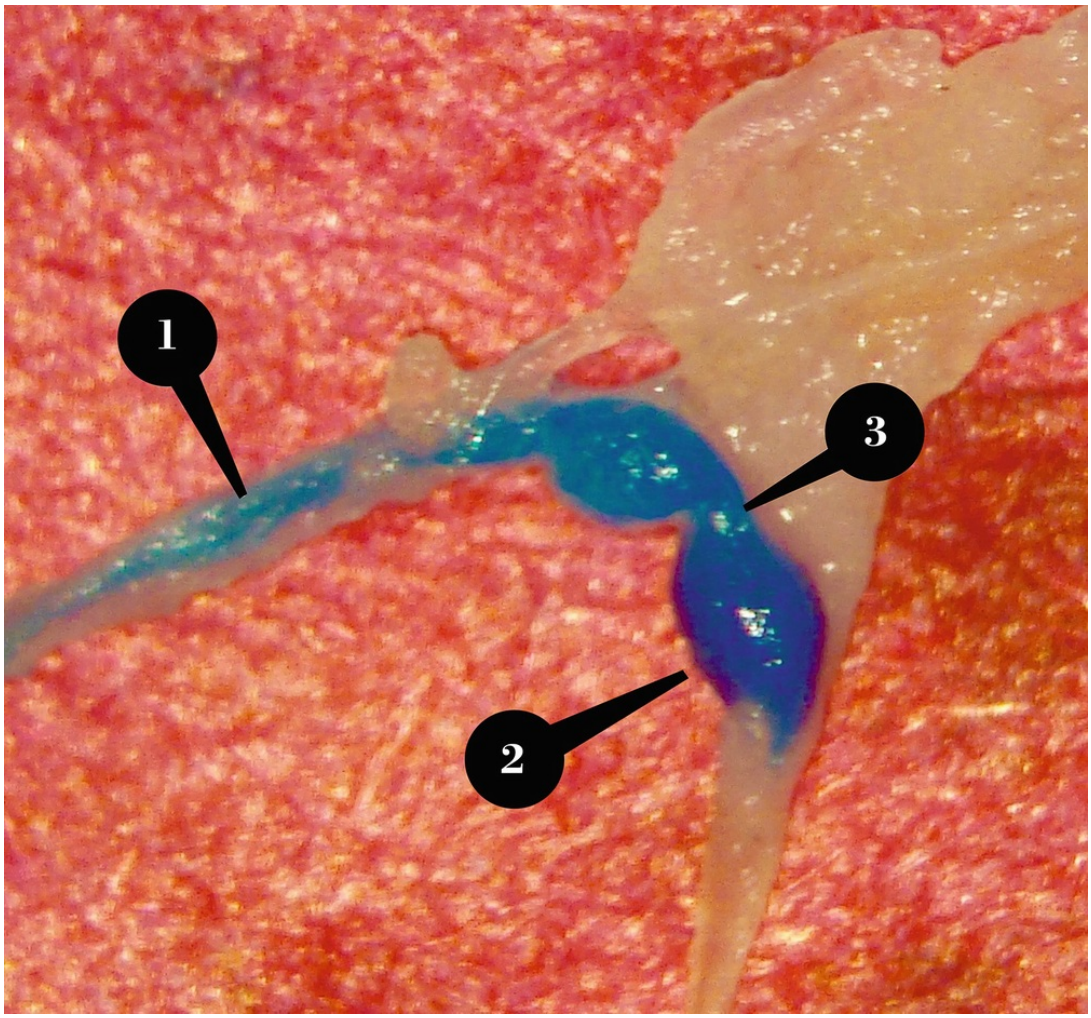

Fig. 1.15 Ex vivo chromolymphography using a surgical microscope. Through a free part of the lymphatic vessel (1) there was injected a coloring material which filled its distal segment. 2 illustrates a clear vascular distention and 3 – lymphatic vessel constriction due to the closing of the valves. The connective tissue layer with vessels is adjacent to the investigated vessel; the layer was not filled with the coloring material

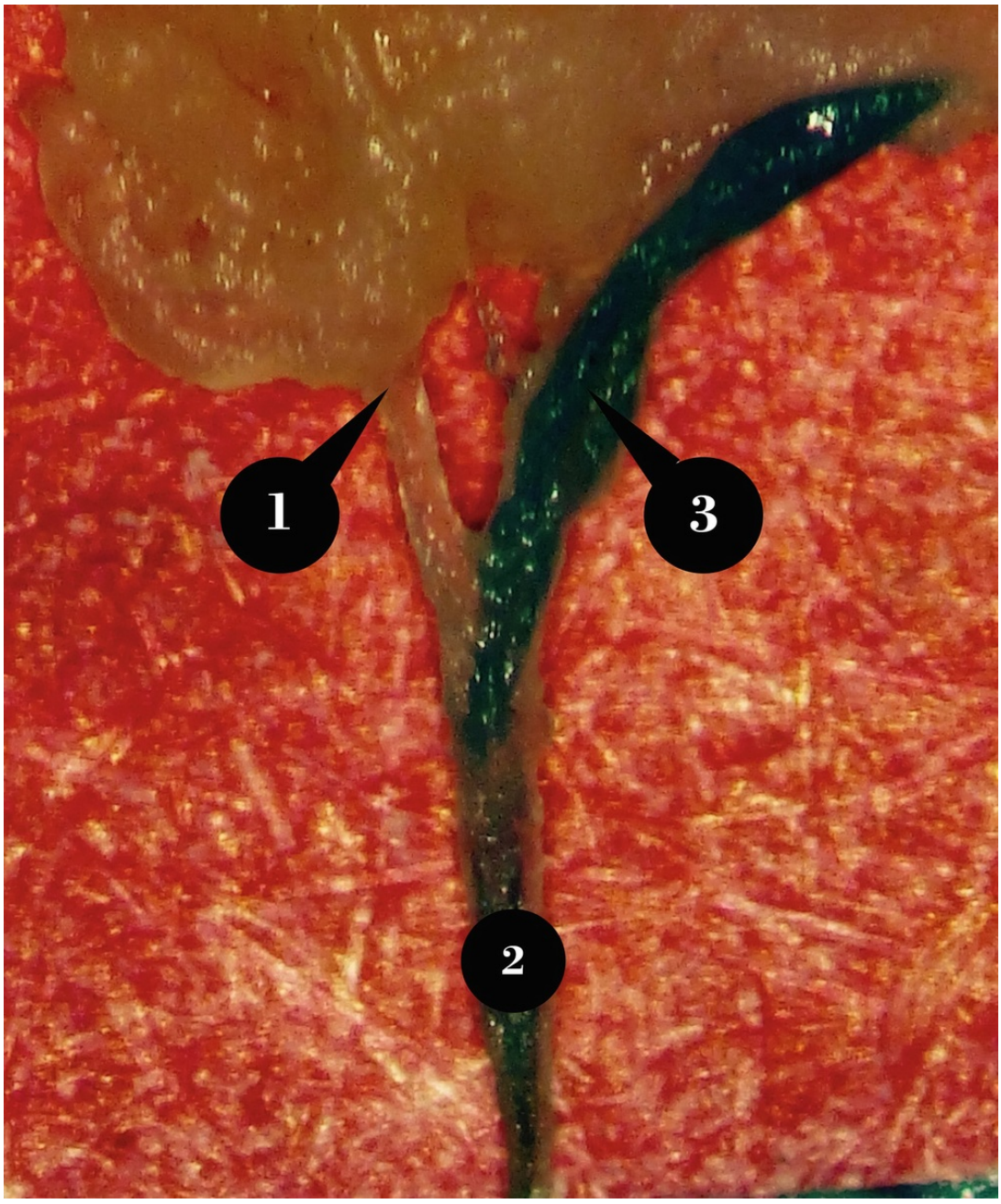

Fig. 1.16 Chromolymphography of inflow vessels of the lymph node. 2 illustrates the main trunk filled with a contrast medium, 1 left branch free from contrast medium, and 3 right branch of the lymphatic vessel which is well contrasted; it has several narrowings along its length

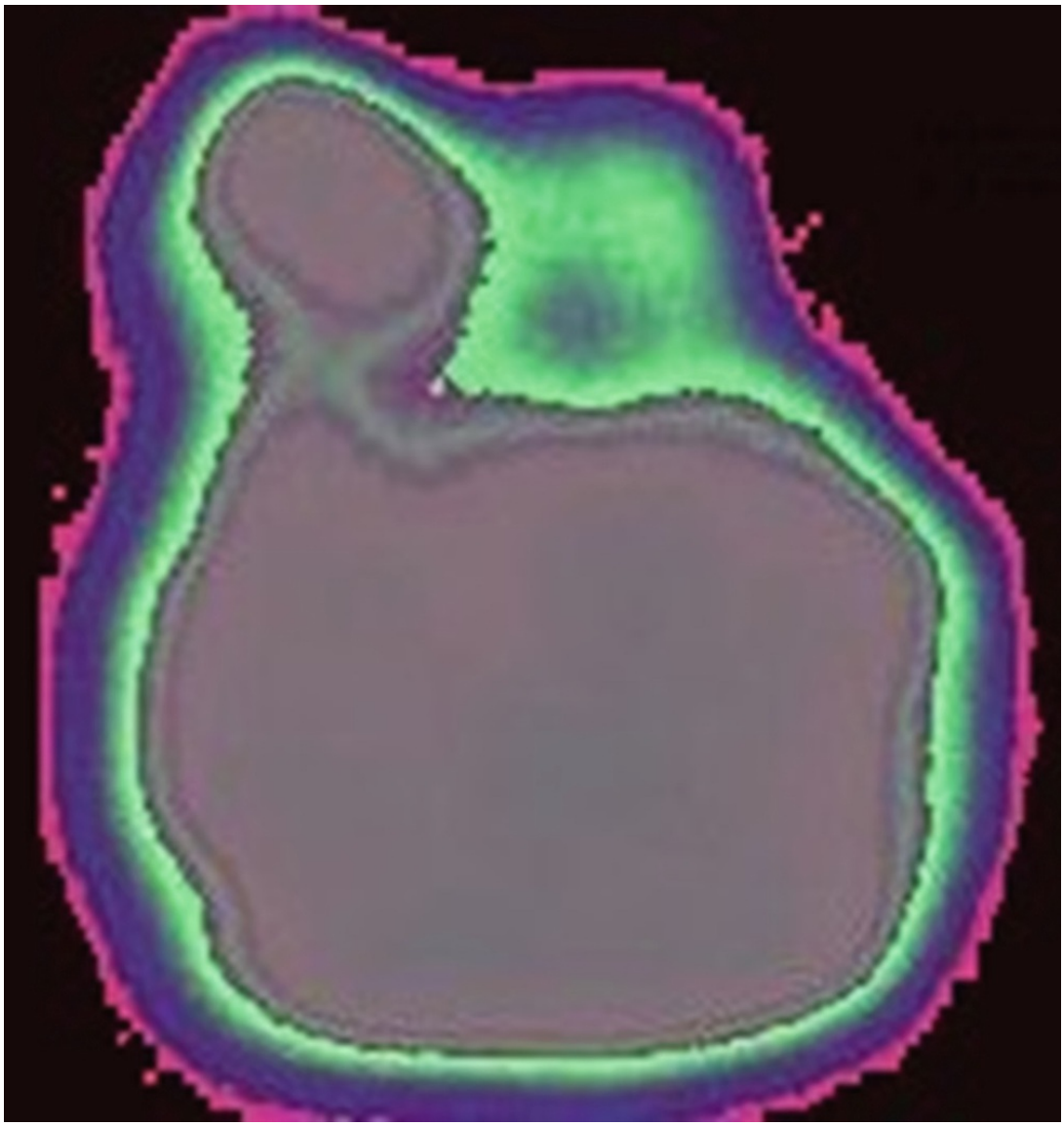

Fig. 1.17 Digital reconstruction of ultrasound investigation of the lymph node: the main pathological process is localized in the capsule, which demonstrates the possibility of its primary metastatic lesion

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2. Lymph Nodes in Cancer: Sentinel Lymph Node

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Keywords Lymphatic system – Axillary lymphatic apparatus – Breast cancer – Metastases – Sentinel lymph node – Sonolipodestruction

The lymphatic system is the anatomical and physiological complex where can be observed dramatic events in oncology diseases. By assessing its status, one can make certain prognosis about the possible course of the disease, take proactive measures to prevent the spread of cancer, and much more. Currently, it is discussed the role of secondary lymphoid organs in the development of cancer and other tumors.

A few decades ago, oncologists proposed that the lymph node that is the closest to the tumor should be called the “sentinel” one

(R.M. Cabanas, 1977). Over the years, this concept keeps its meaning. Today, Cabanas theory can be discussed from various points of view, but it seems to us that the discovery of this stage prompted deeper and more comprehensive research, which resulted in a rethinking of lymphatic dissection scope and even surgeries of the primary tumor. All these scientific results fall into the paradigm shift platform in oncology, which opens up prospects for sparing treatment and improved long-term results. It can be concluded that oncologists' attitude to lymphatic organs in cancer is a marker of a real and systemic review of therapeutic and diagnostic doctrine.

It can be assumed that the data we obtained will also serve this process.

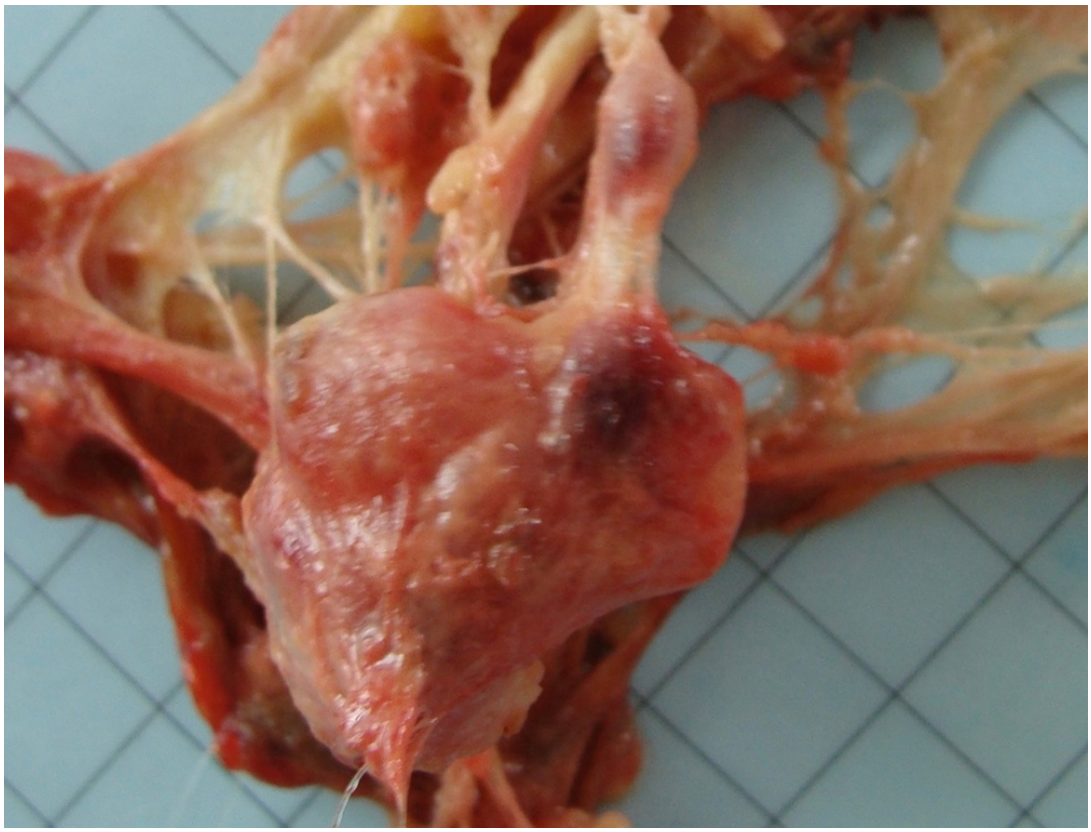

Fig. 2.1 Native lymph node isolated by ultrasonic dissection; it is totally affected by cancer metastases. The capsule bulges out due to the growth of metastatic nodules. Neo-lymphangiogenesis is not active; paranodular

vessels are well-formed

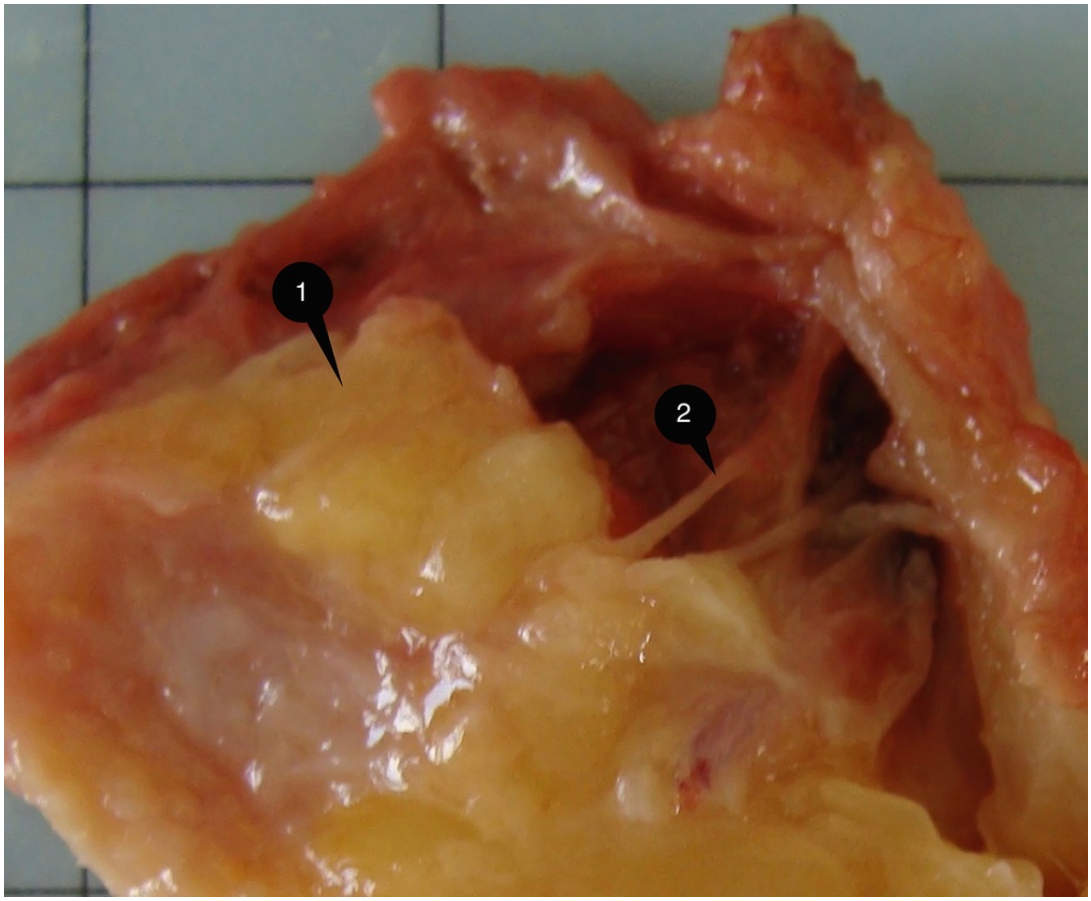

Fig. 2.2 Ultraselective dissection of the lymph node affected by tumor process. In the advanced stage of cancer, a thickening of the capsule is observed; it can be easily isolated from the lymphoid tissue. Figure 1 illustrates the lymphoid tissue with elements of adipose degeneration and 2 – microcirculation vessels outflowing from the capsule into the thickness of the node

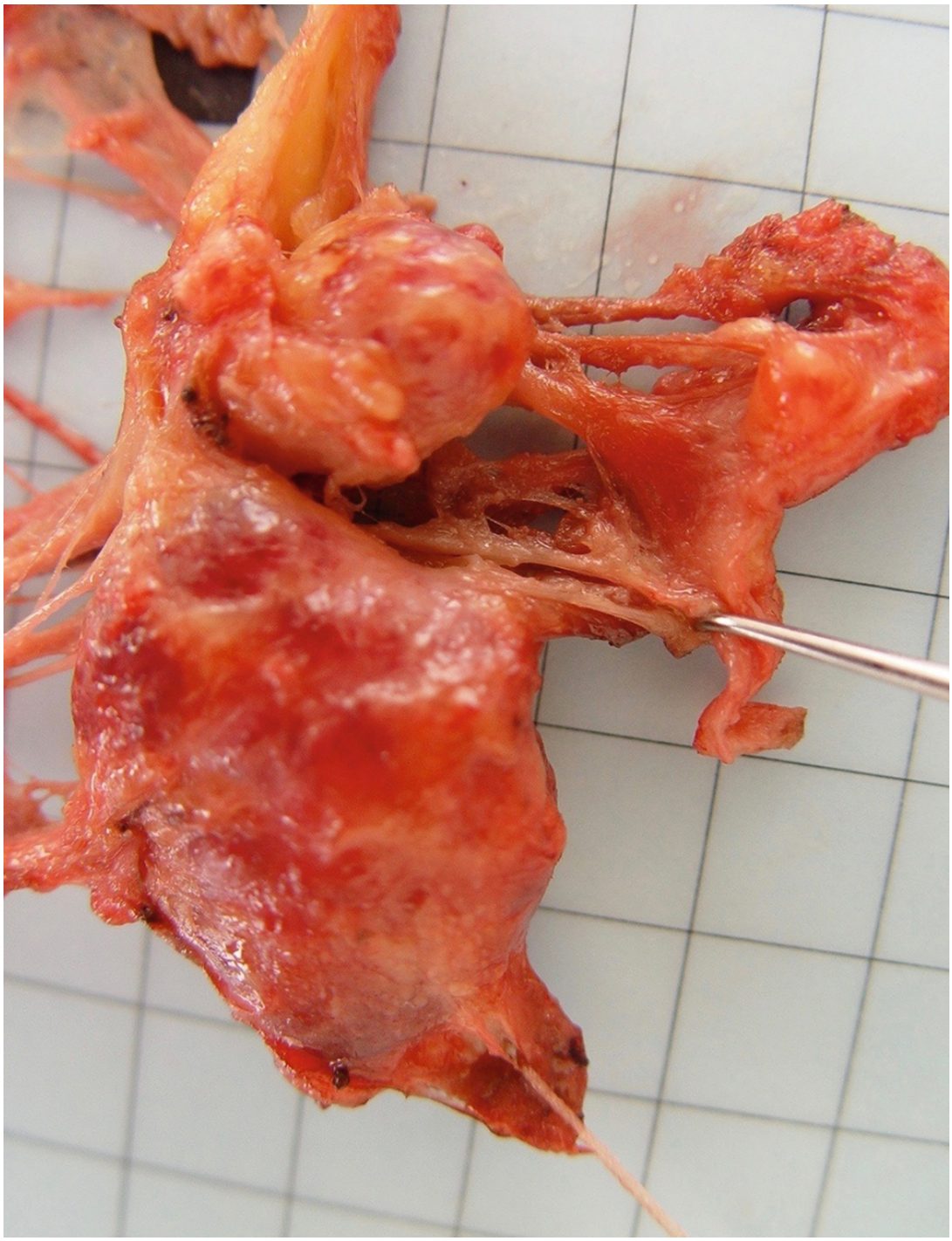

Fig. 2.3 Lymph node with signs of metastatic lesion. The node size is 40 mm in length. The capsule is inhomogeneous and tuberous. The node is adhered to surrounding tissues. Neo-lymphangiogenesis is not active

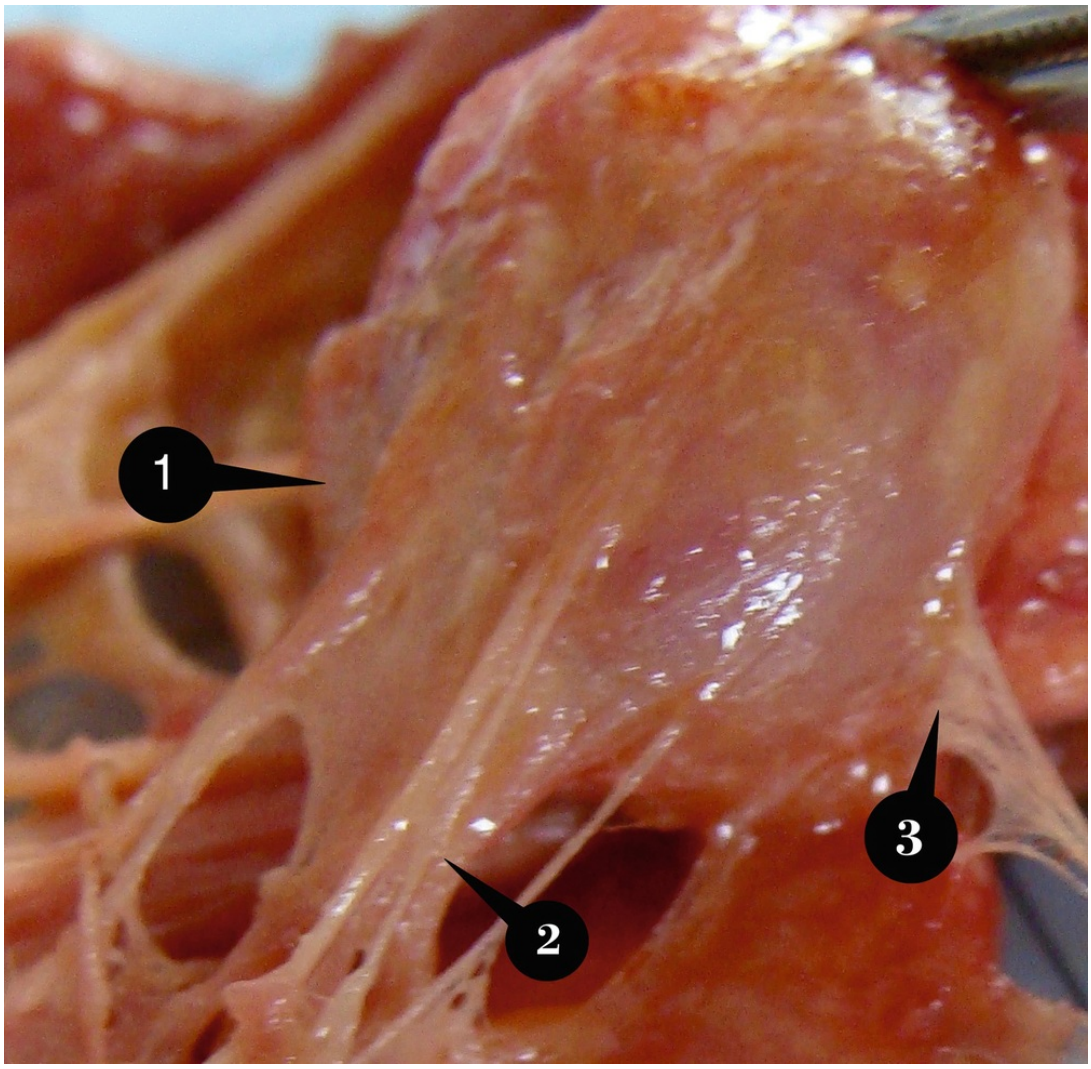

Fig. 2.4 The fragment of the lymph node (1) in breast cancer and multiple vessels (2, 3) providing node drainage

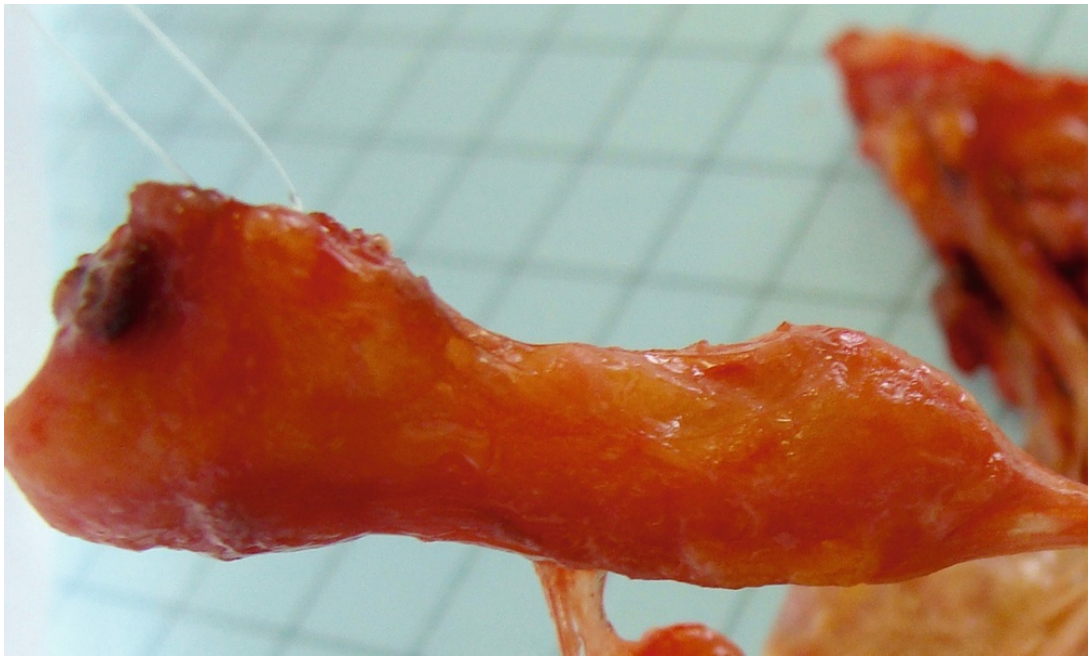

Fig. 2.5 Lymph node affected by metastatic disease, as evidenced by shape, size, and consistency. The capsule is inhomogeneous, with focal dystrophic changes. Neo-lymphangiogenesis is not active

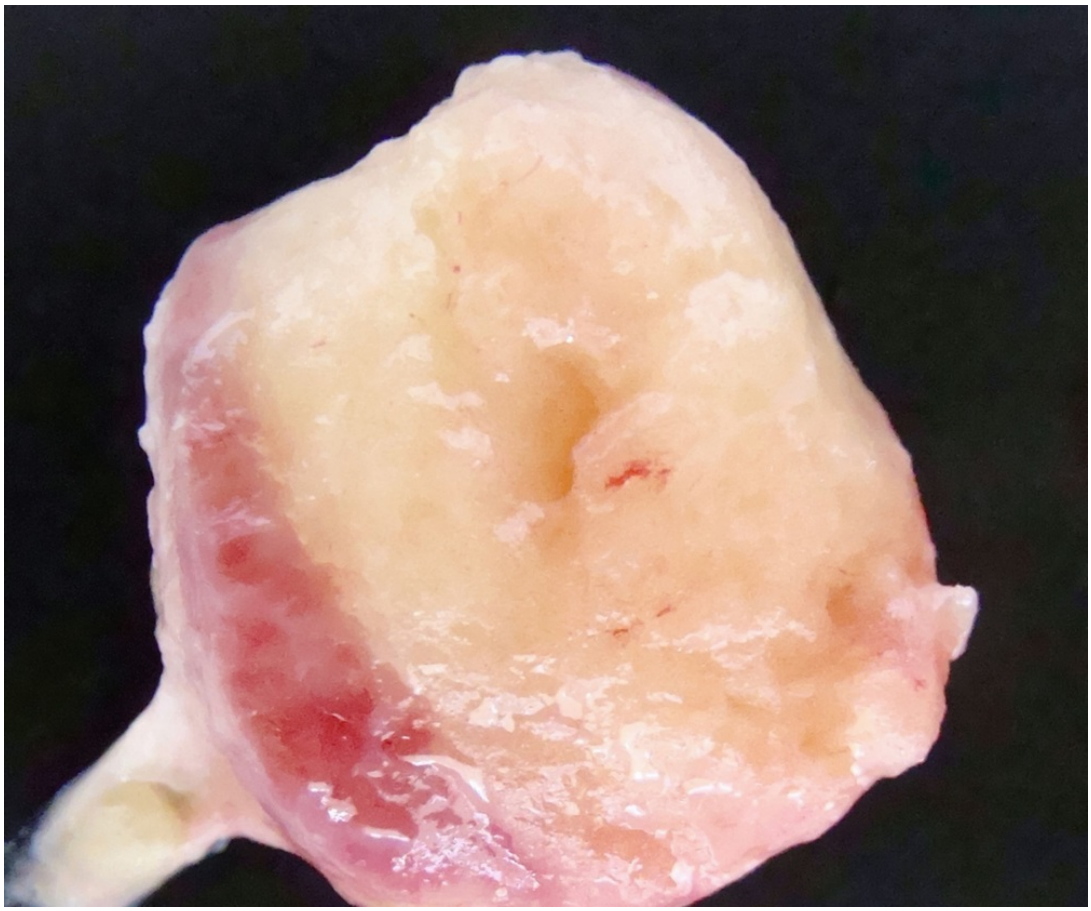

Fig. 2.6 Transverse section of the lymph node, 90% of which is filled with metastatic mass

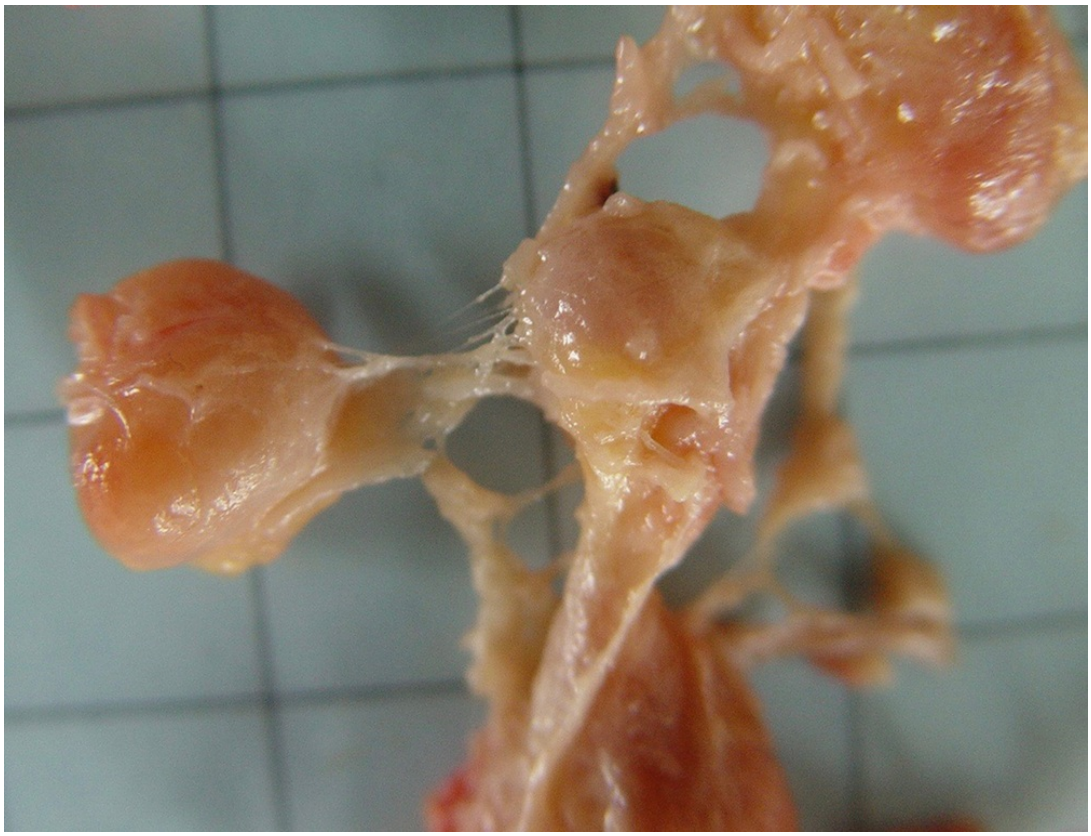

Fig. 2.7 Lymph node glomus connected with each other by native and newly formed vessels

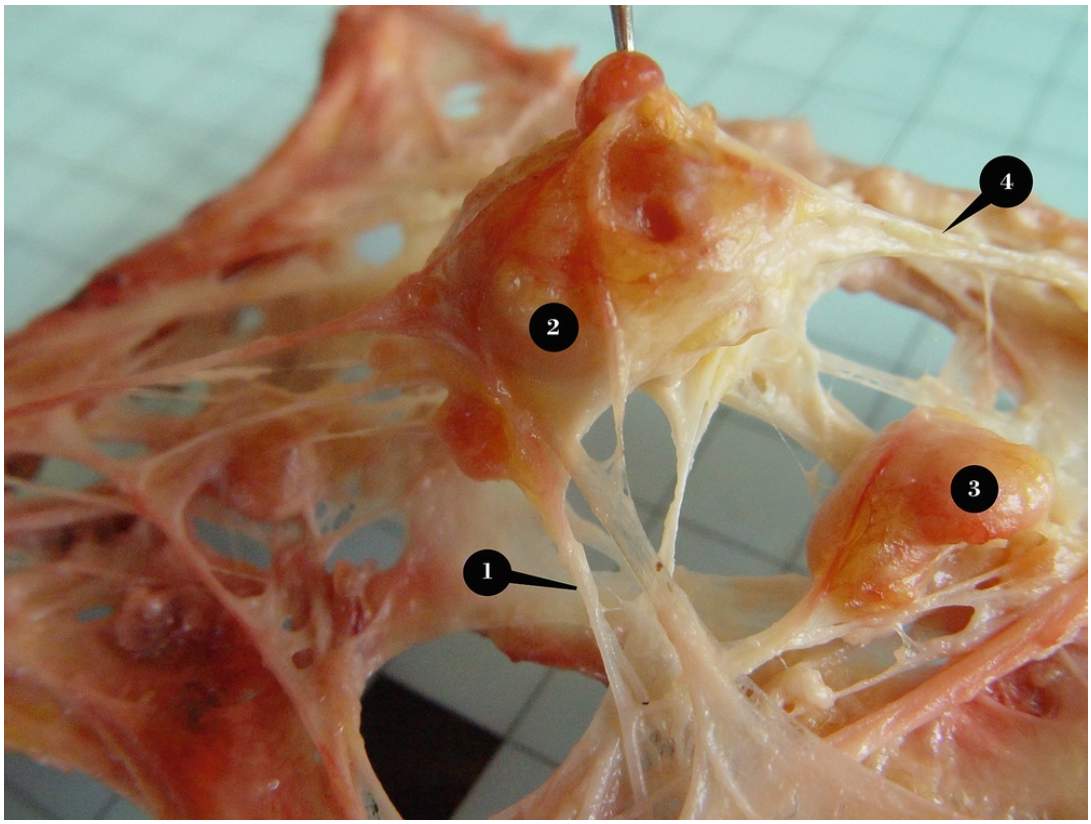

Fig. 2.8 The components of lymphatic mapping in breast cancer. Figures 2 and 3 illustrate the lymph nodes and 1, 4 – lymphatic vessels. The 1 lymph node is elevated upward with a hook

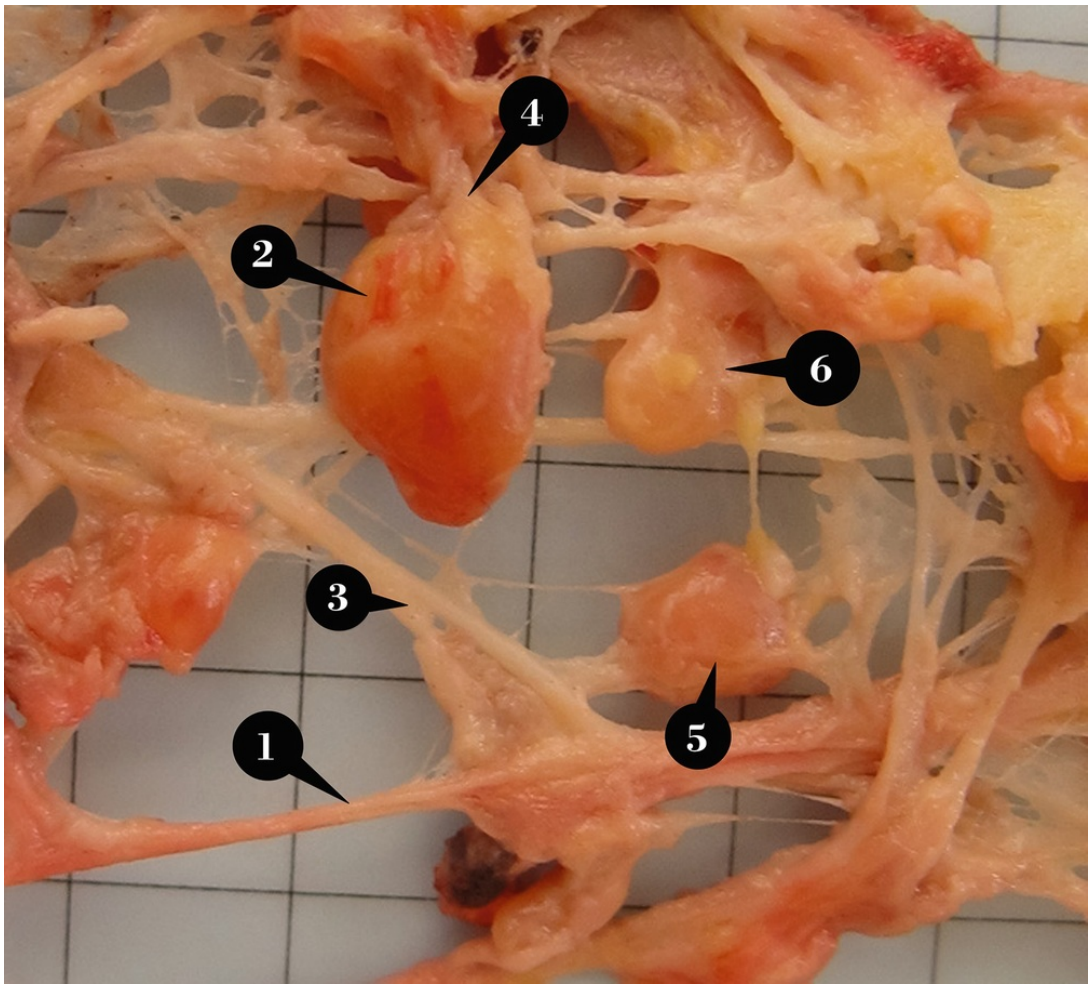

Fig. 2.9 There is a group of lymph nodes in the specimen (stage III breast cancer). The largest lymph node (2) is heart-shaped. Other lymph nodes (5, 6) are of smaller size and outwardly resemble tertiary nodes (newly formed) . Figures 1 and 3 illustrate the lymph node basins

Fig. 2.10 A group of lymph nodes isolated by ultrasonic lymphatic dissection. The nodes are spherical, up to 10 mm. The lymph node capsule has a different degree of pathological transformation. Neo-lymphangiogenesis is not active. The great vessels are well-formed

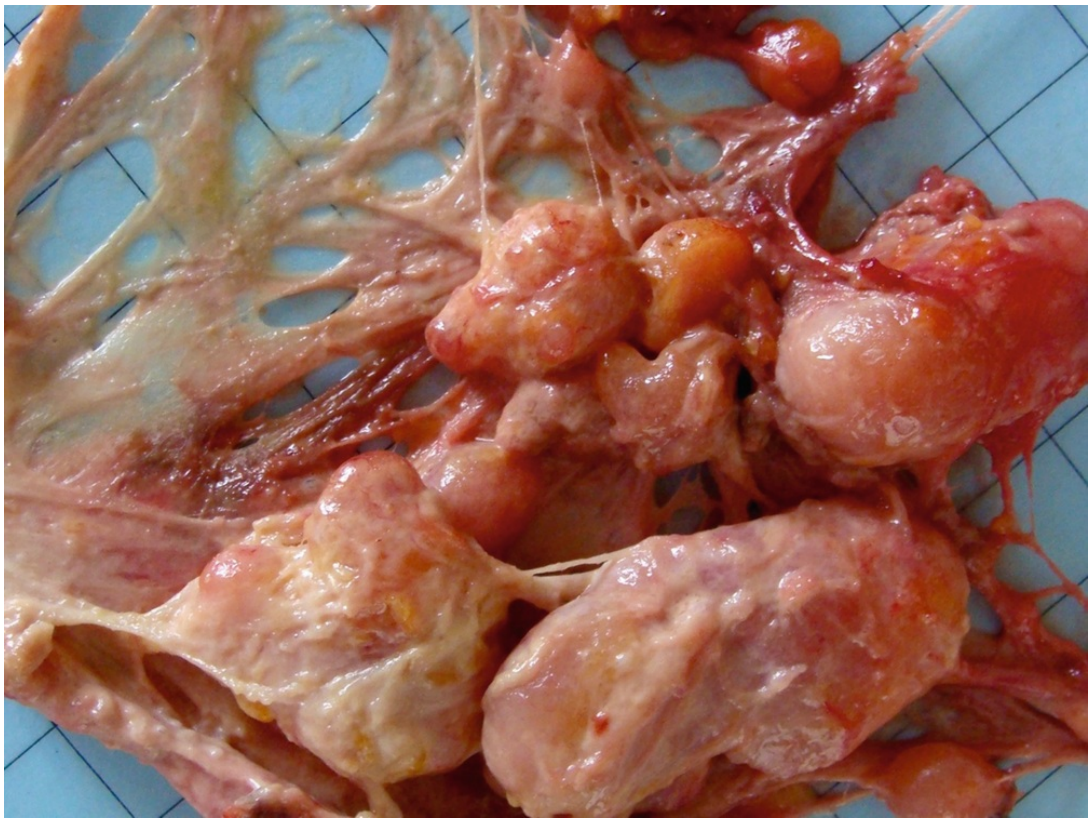

Fig. 2.11 Cascade of lymph nodes, some of which have signs of metastatic lesion. The nodes' size ranges from 10 to 30 mm. Lymph node capsules are inhomogeneous in structure and color. The stromal component is represented by a network of well-formed lymphatic vessels

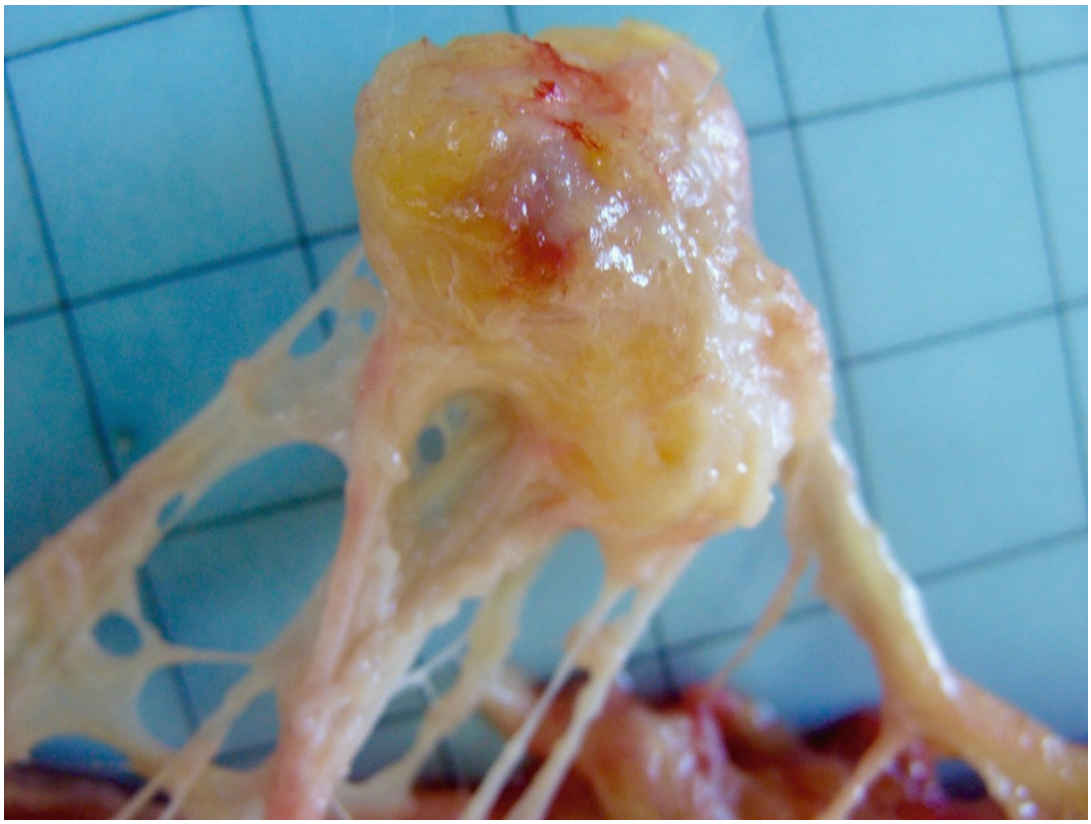

Fig. 2.12 A single lymph node with a well-formed inflow vessel component. Vessels are not enlarged. The capsule contains a significant amount of adipose tissue

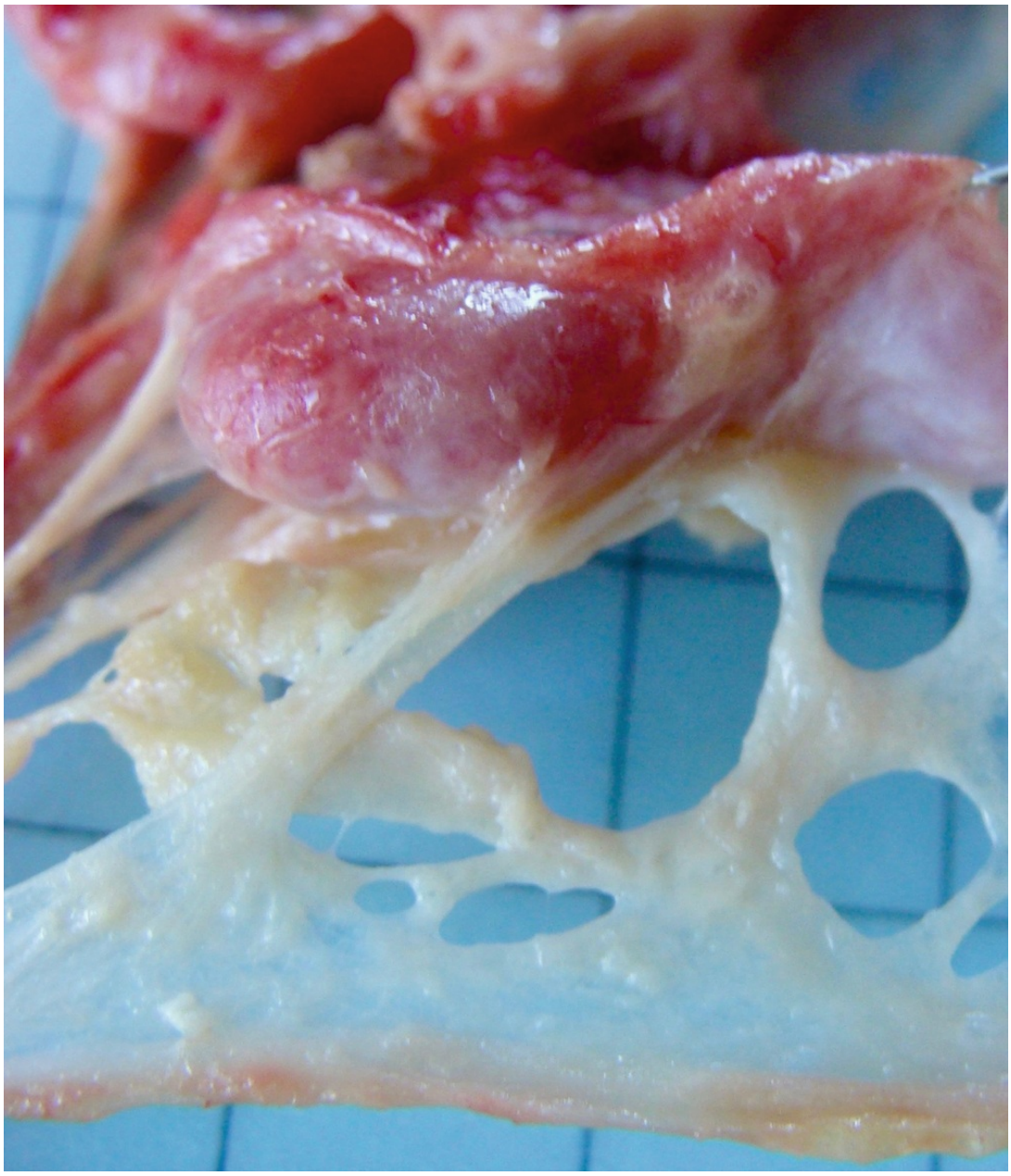

Fig. 2.13 There is the lymph node surrounded by a well-developed network of lymphatic vessels. The vessel lumen is enlarged. The lymph node is enlarged; the capsule is hyperemic

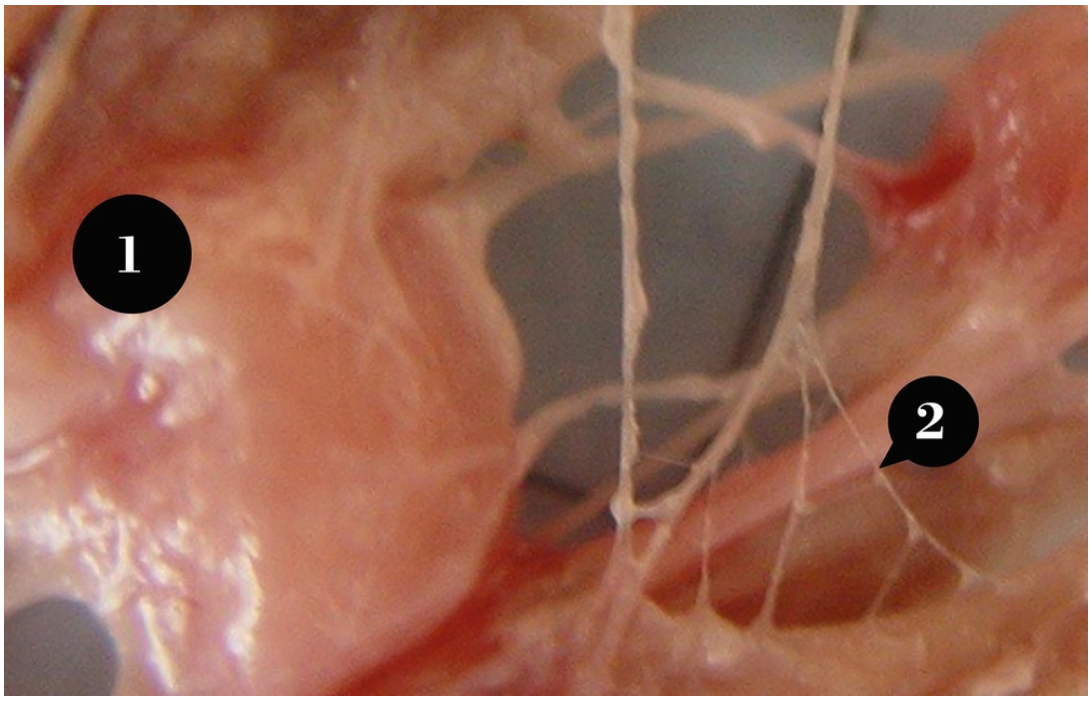

Fig. 2.14 The fragment of the lymph node (1) and newly formed vessels (2). The lymph node capsule is pale; there are vessels beneath it. The newly formed vessels form a network of microcapillaries

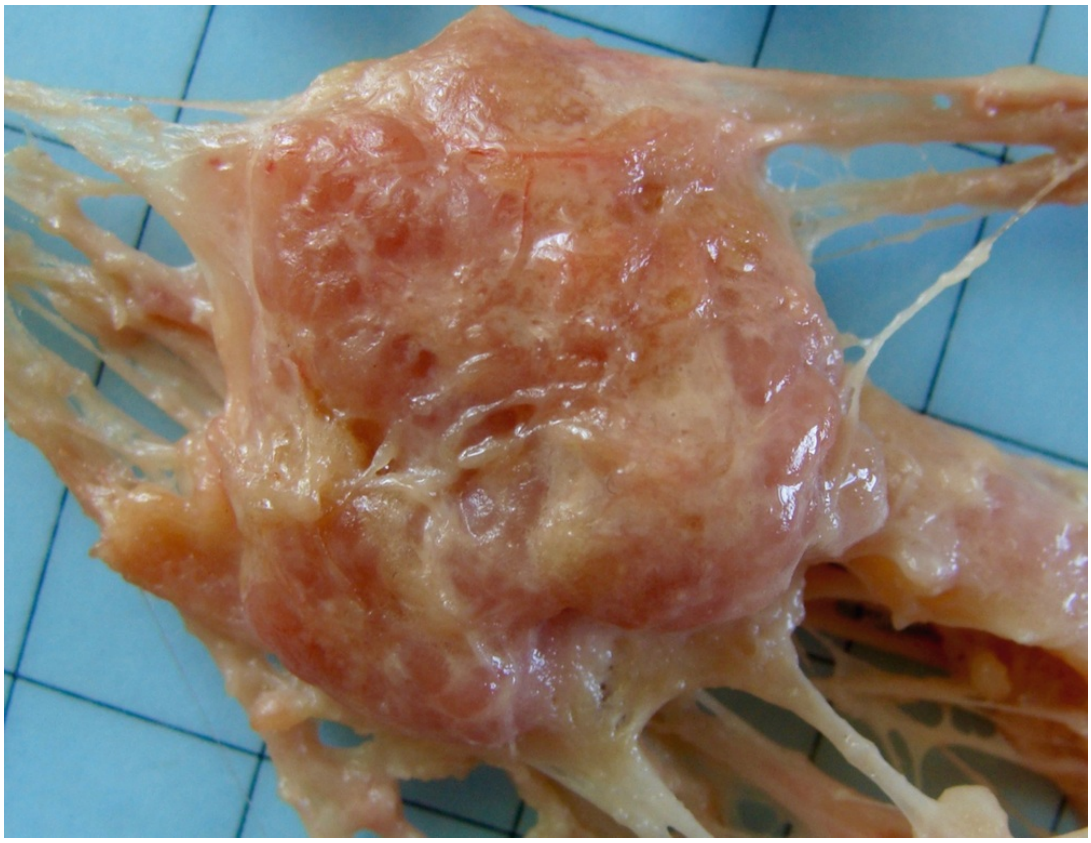

Fig. 2.15 Sentinel lymph node. The node size is about 20 mm, it is surrounded by a considerable number of lymphatic vessels of various diameters, and some of them exceed 3 mm. The node capsule is tuberous and inhomogeneous, with pale areas

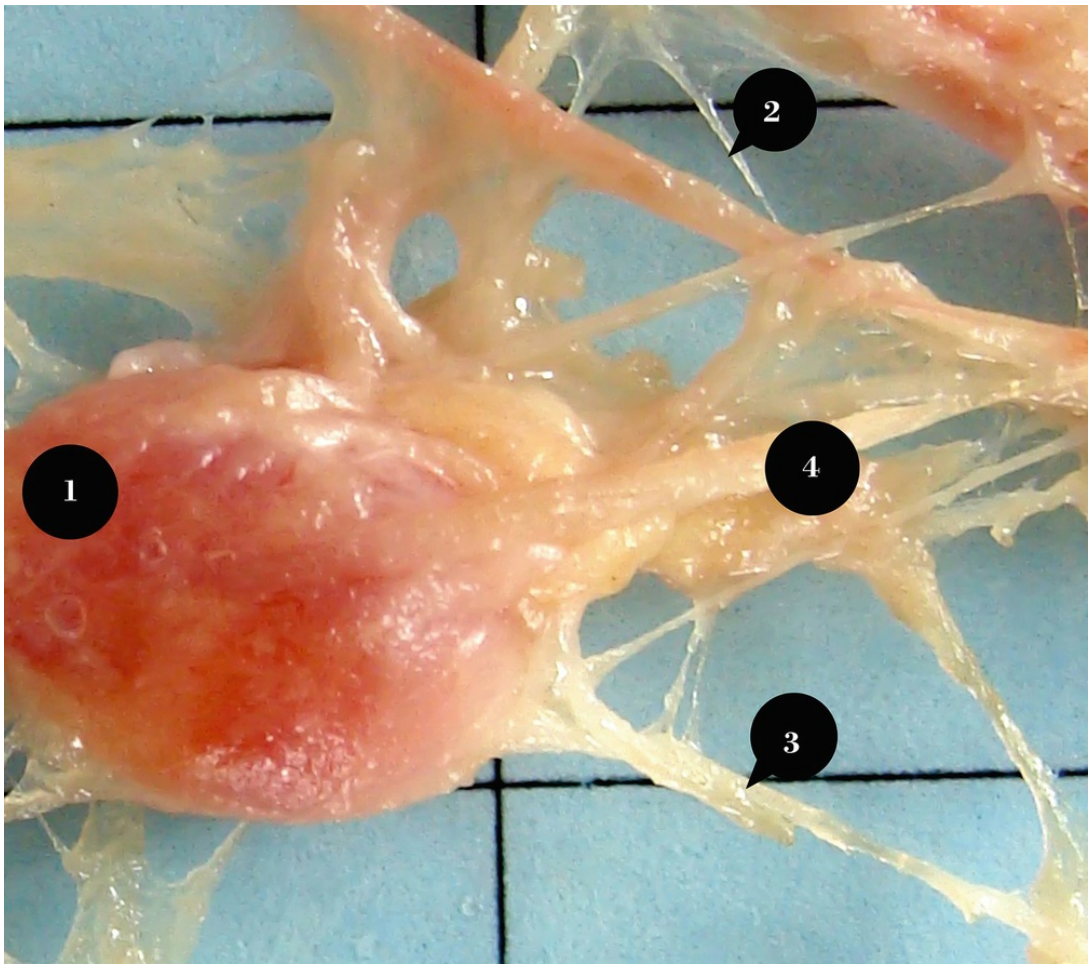

Fig. 2.16 The fragment of the lymph node with signs of metastatic lesion (1) – sentinel lymph node. Figures 2, 3, and 4 illustrate the vascular system providing blood supply and drainage of the lymph node. The lymphatic vessel 2 is connected with adjacent intervascular anastomoses

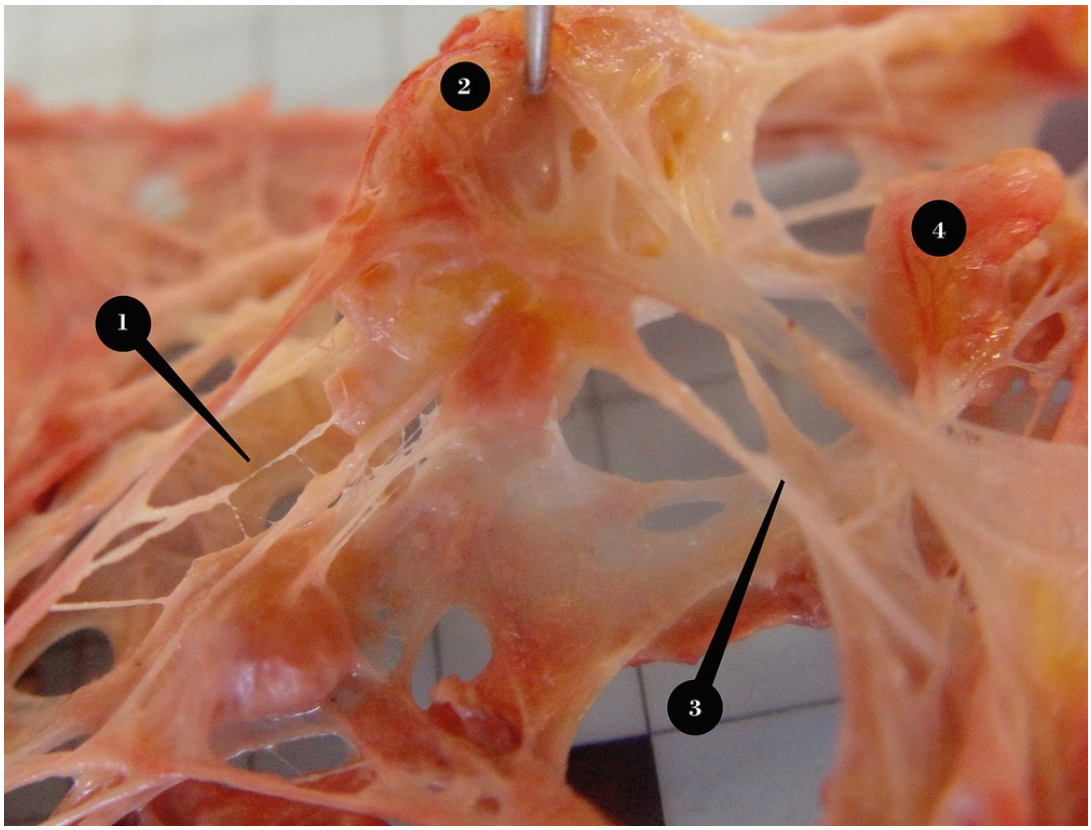

Fig. 2.17 Sentinel lymph node (2) with a large number of newly formed vessels (1,3). The stromal component is massive. Figure 4 illustrates a second-order node providing further lymphatic transit

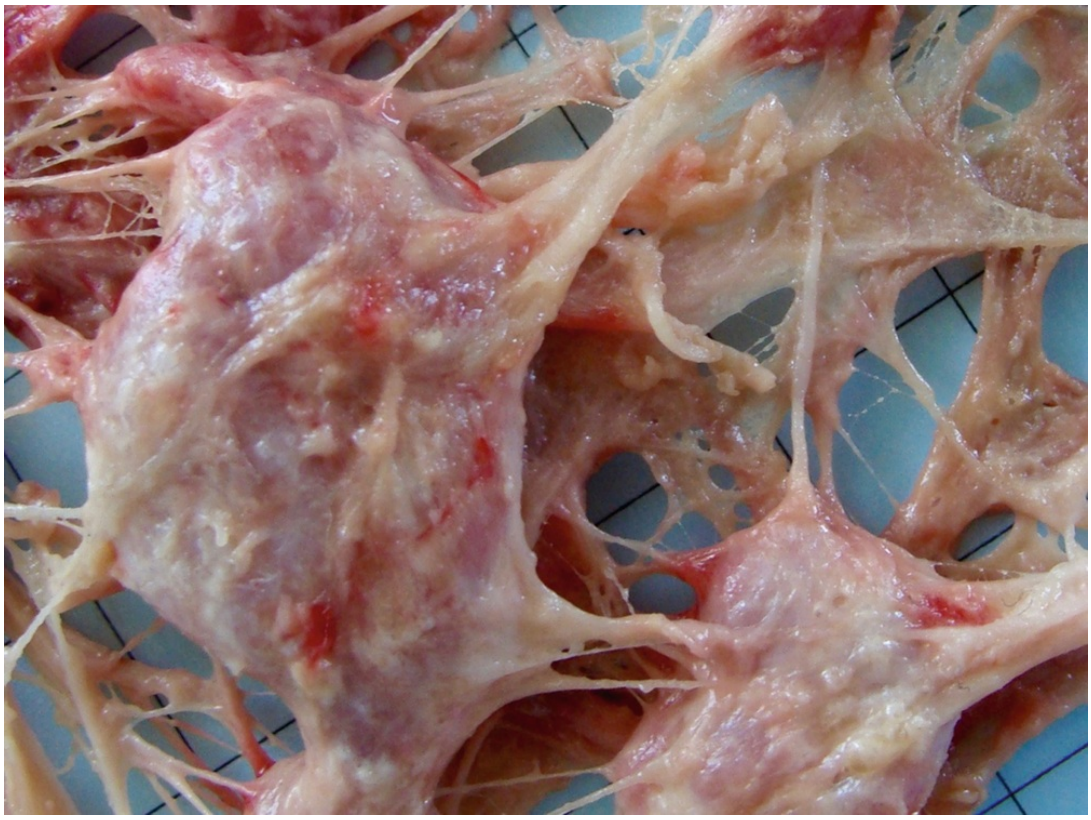

Fig. 2.18 Sentinel lymph node in breast cancer. The node size is 40x20 mm. The capsule is inhomogeneous and pale, with fat deposits. Similar node is attached to the sentinel one, but is of smaller size. Neo-lymphangiogenesis is active

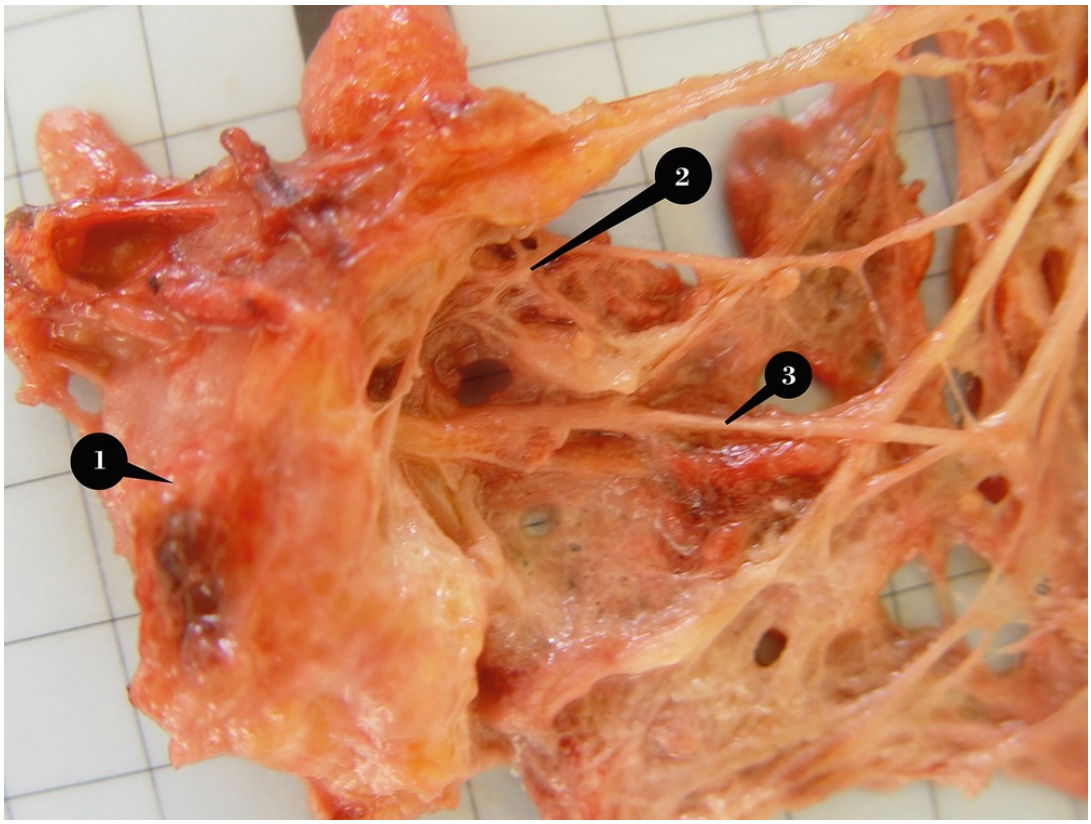

Fig. 2.19 The sentinel lymph node (1) is of irregular shape and 40x20 mm in size, its capsule is heterogeneous, and pale portions alternate with the zones of vascular injection. The node hilus is wide and reaches 15 mm (at the 12 o'clock position on the dial). Figures 2 and 3 illustrate native lymphatic vessels of different diameters. The stromal component is expressed

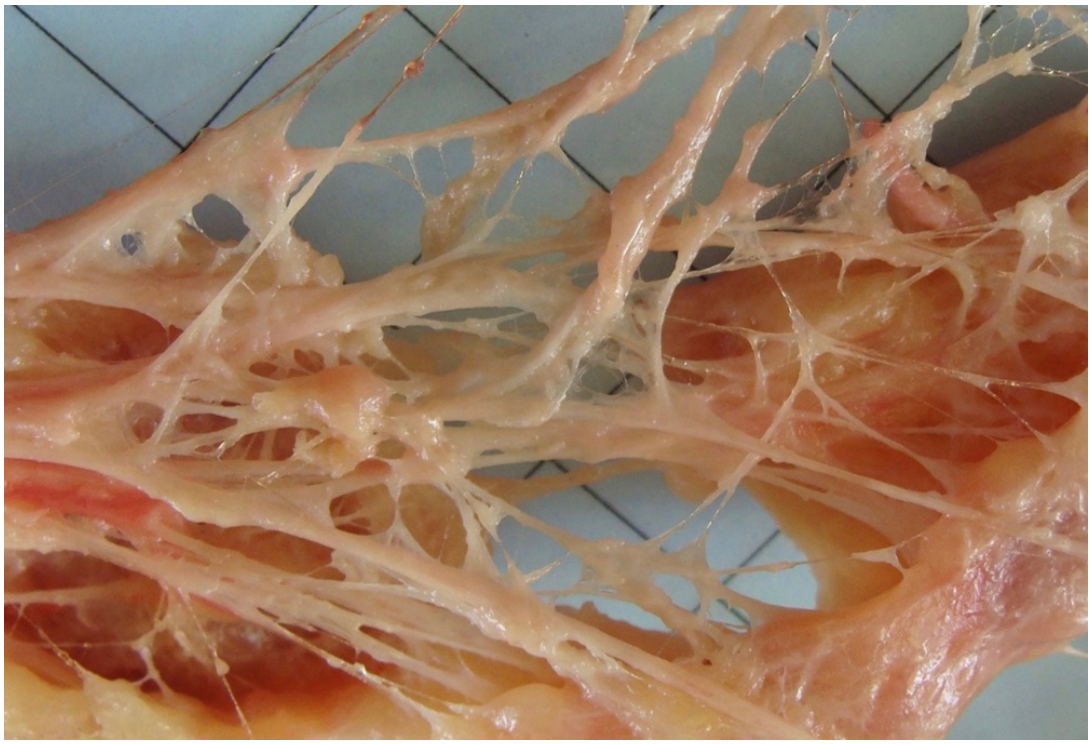

Fig. 2.20 Vasculature of axillary region after ultrasonic dissection in cancer. The vascular density is significant. Vessels differ in diameter; in some places constrictions are interchanged with distentions and thickenings. There are a large number of newly formed lymphatic vessels. The sentinel lymph node with a large number of inflow vessels is visible at the 17 o'clock position on the dial

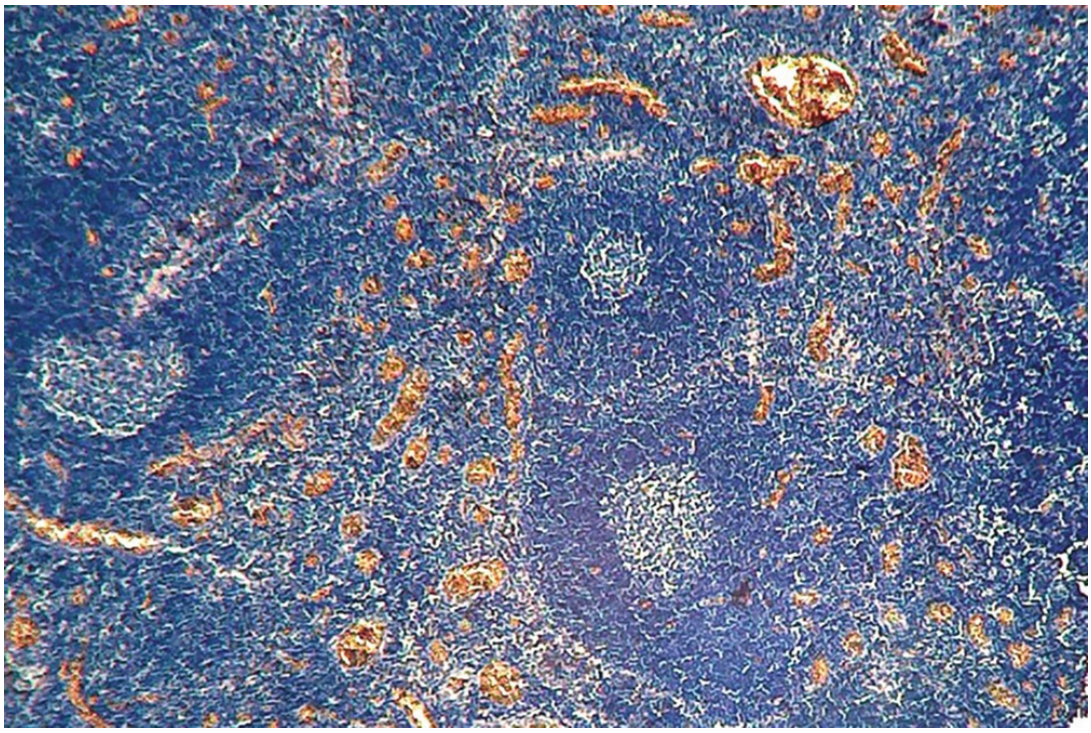

Fig. 2.21 Lymph node. Blood vessels are filled with formed elements. Hematoxylin and eosin stain

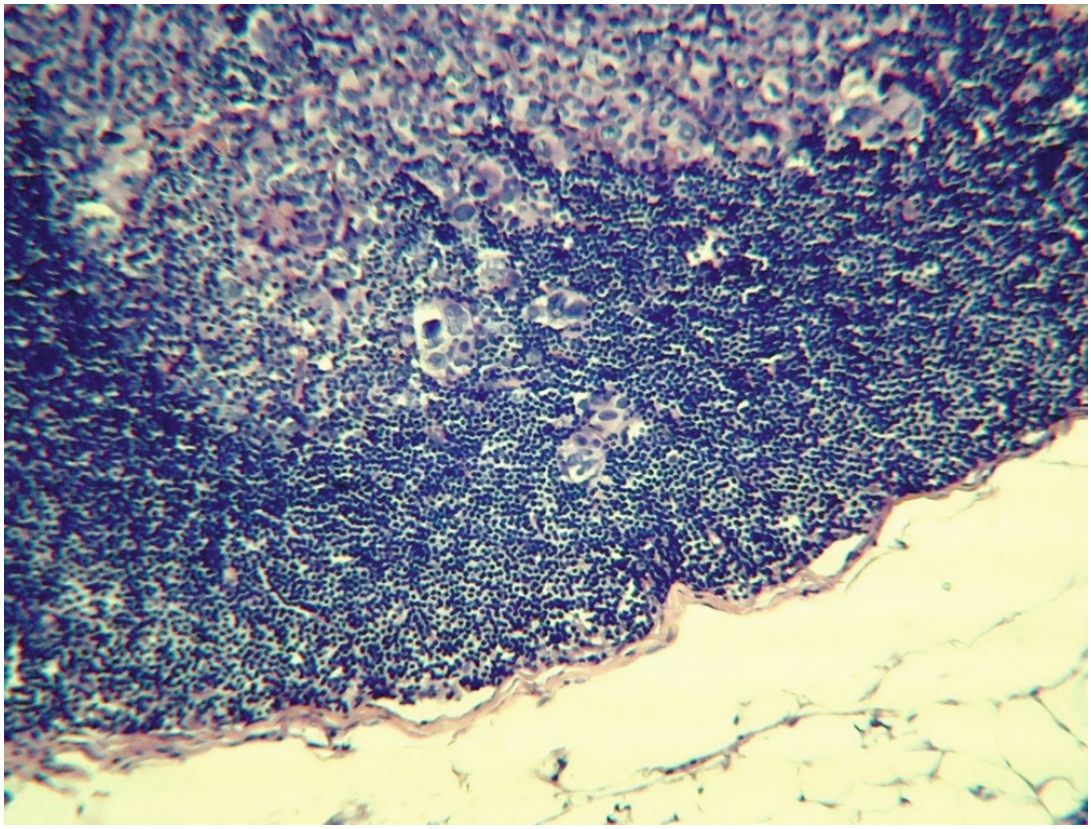

Fig. 2.22 Tumor expansion of the lymph node in breast cancer. The spread of pathologic process in a distal direction. There are metastatic cells in lymph capillaries. Density of lymphocytes in the node tissue (outside tumor mass) is high. Hematoxylin and eosin stain

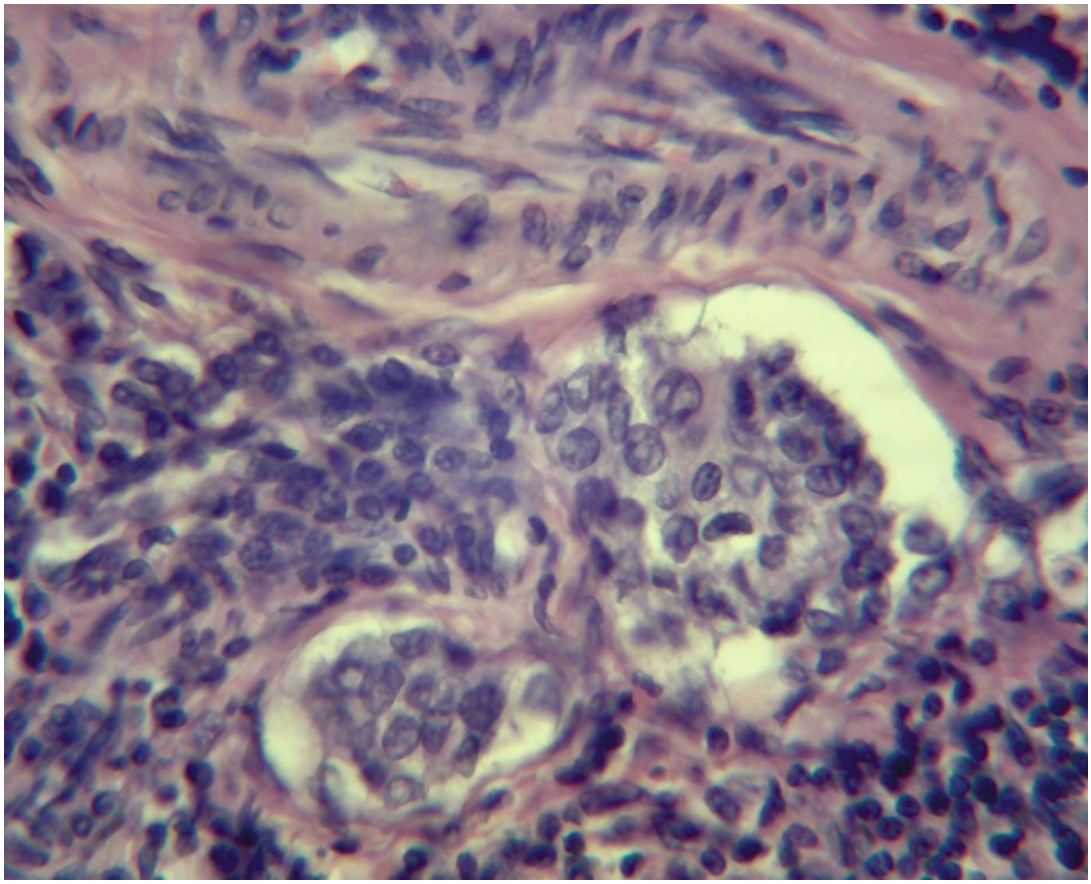

Fig. 2.23 Breast cancer metastasis involving vessels and tissue of the lymph node. Hematoxylin and eosin stain

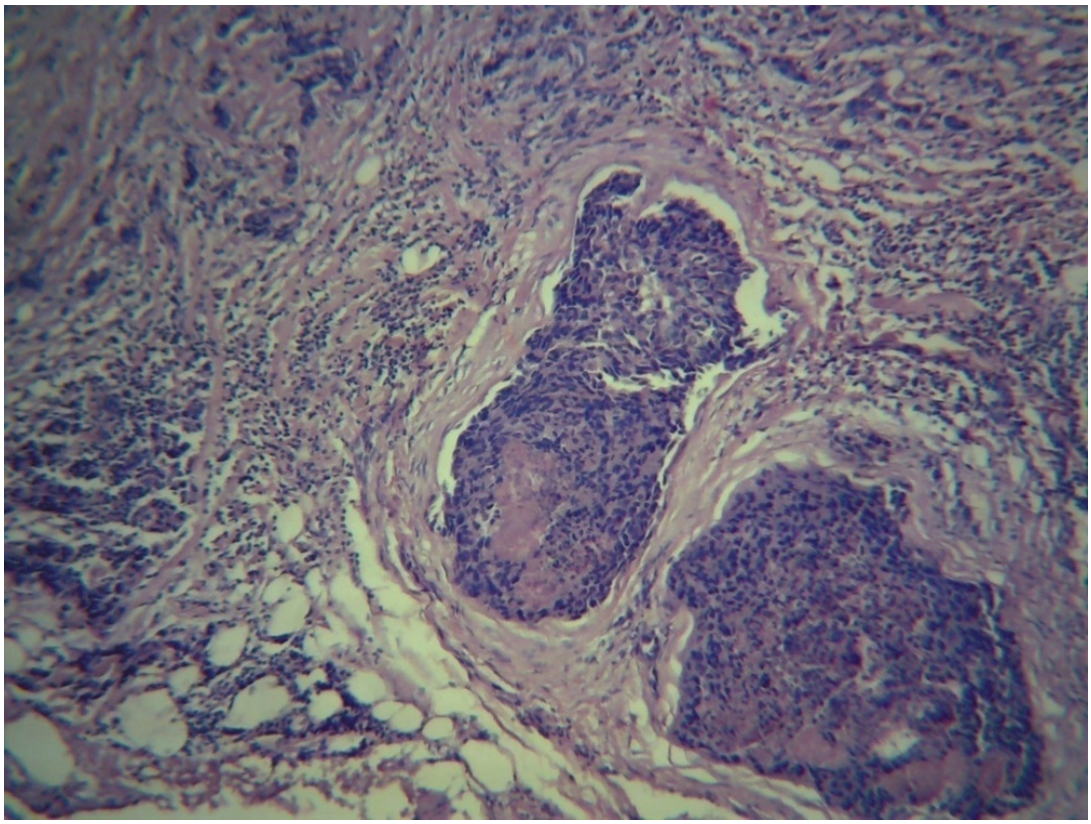

Fig. 2.24 Lymph node with cancer metastases. Total occlusion of lymphatic microcirculation vessels by tumor cells. Hematoxylin and eosin stain

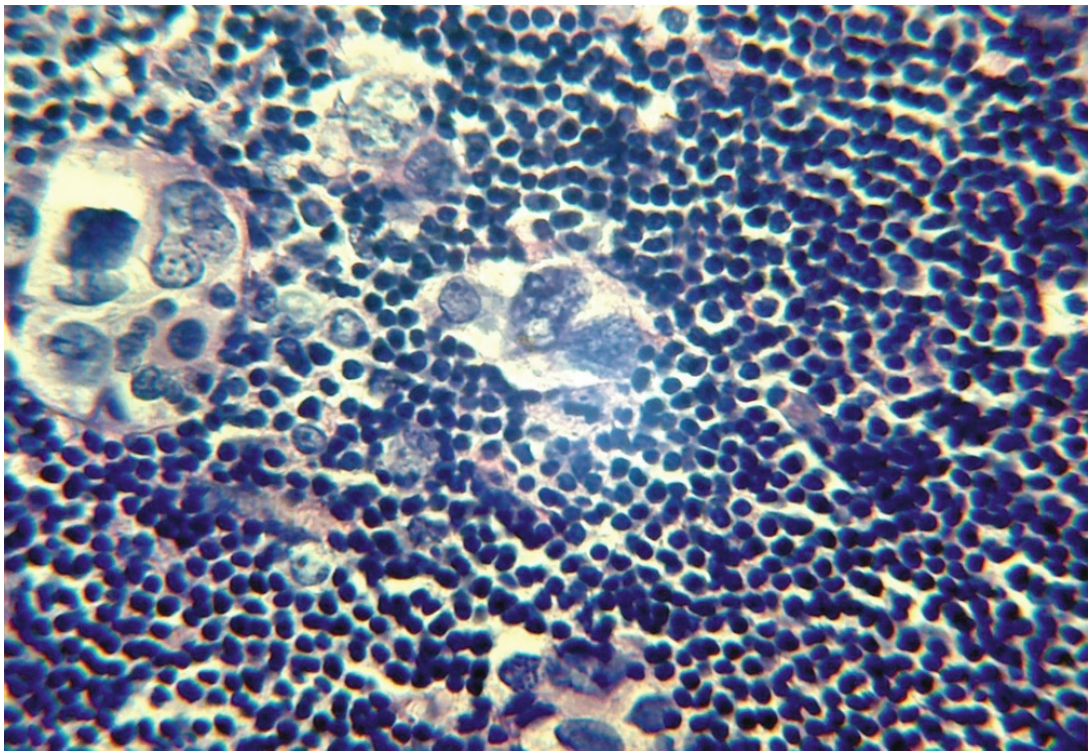

Fig. 2.25 Lymph node with cancer metastases. The vessels are filled with cancer cells. Single cancer cells in the node tissue. Hematoxylin and eosin stain

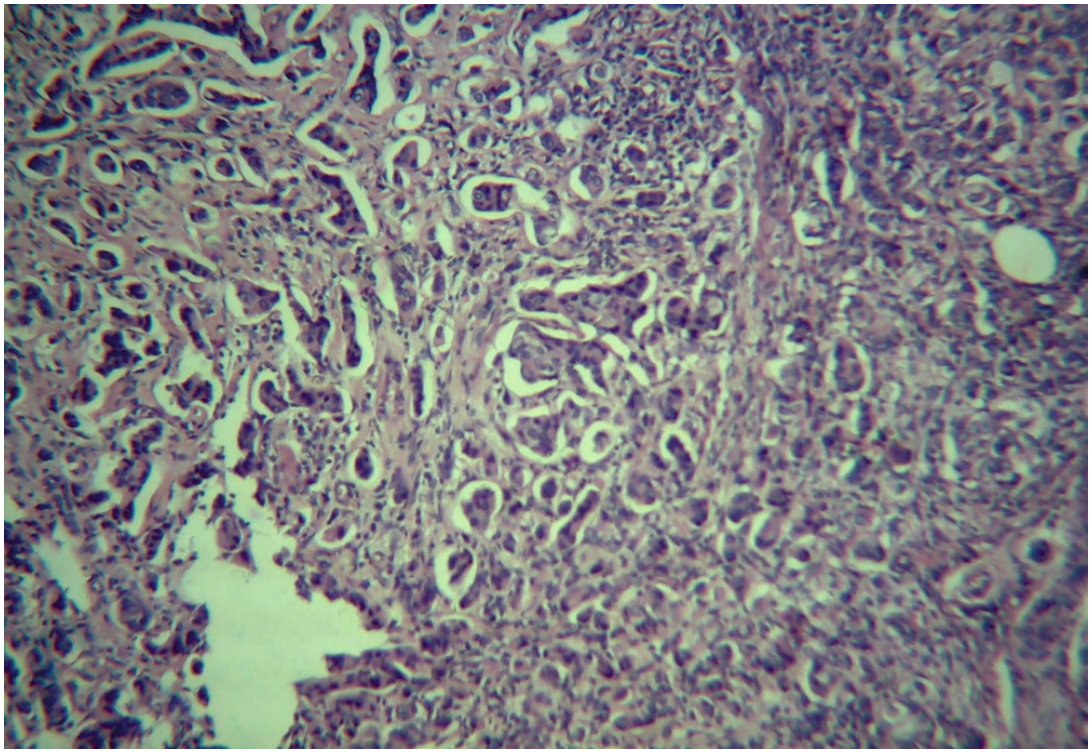

Fig. 2.26 Multiple tumor emboli in the lymph node vessels. There are practically no visible lymphocytes. Total perfusion block. Hematoxylin and eosin stain

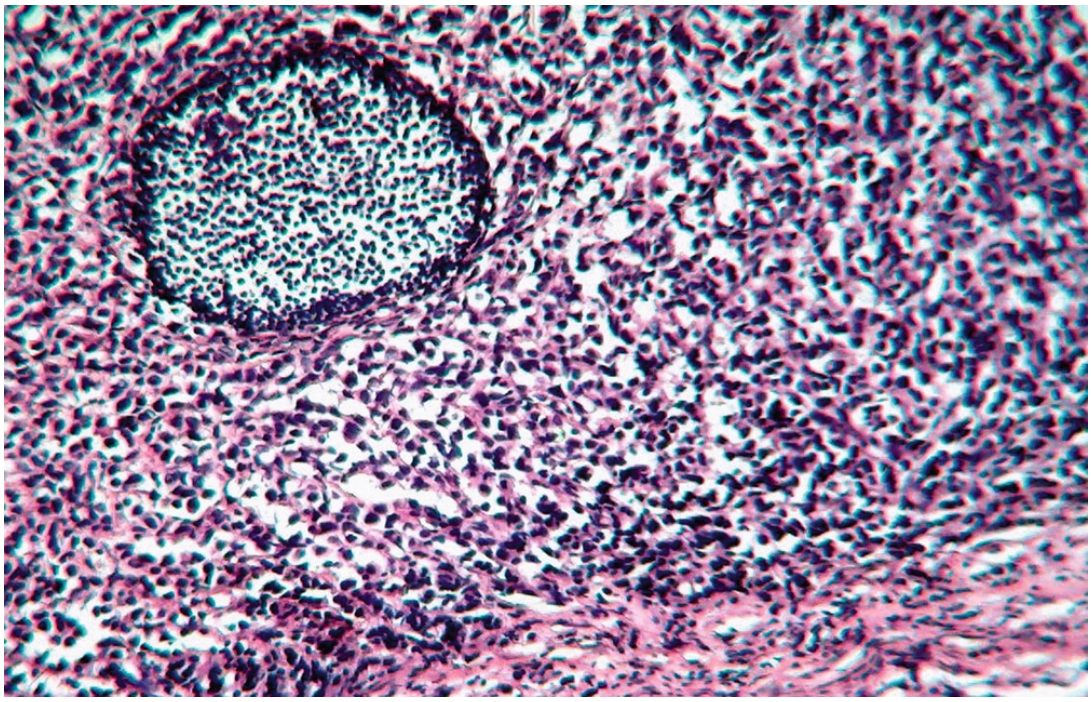

Fig. 2.27 Tumor invasion of the lymph node in breast cancer. A natural barrier formed around lymphocytes prevents necrocytosis of the immune system. Hematoxylin and eosin stain

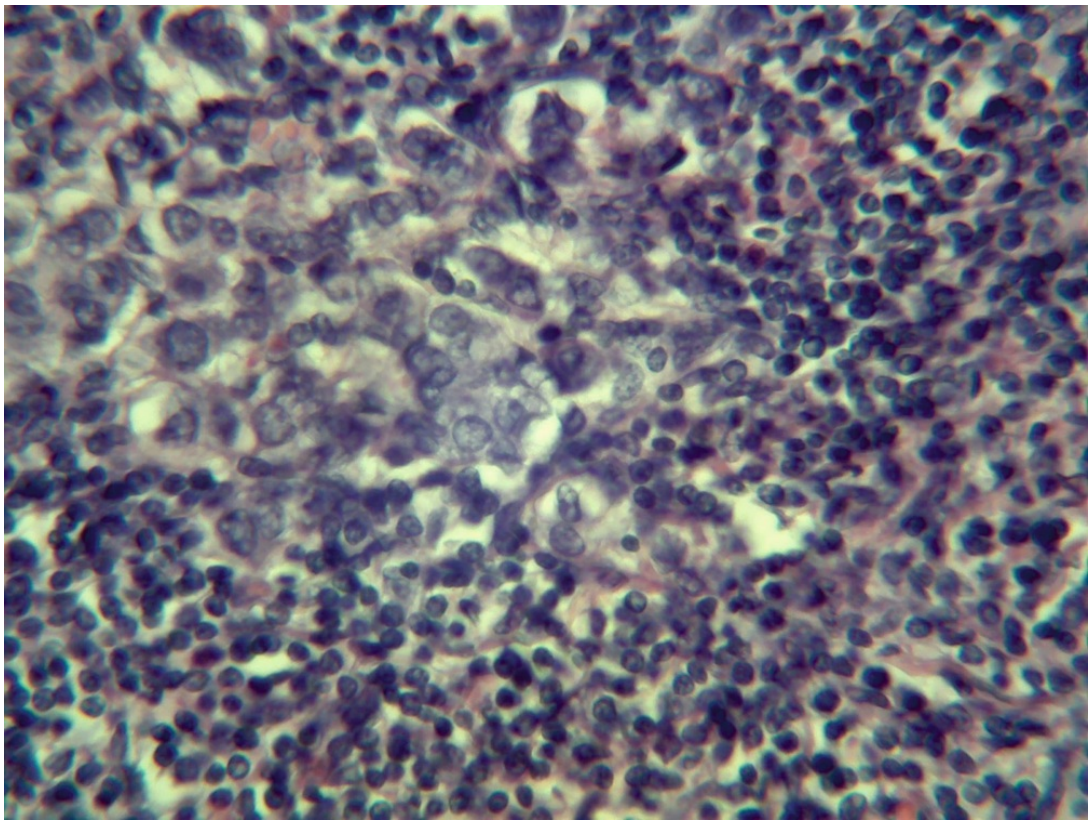

Fig. 2.28 A colony of cancer cells in the lymph node parenchyma surrounded by a variety of lymphocytes. Hematoxylin and eosin stain

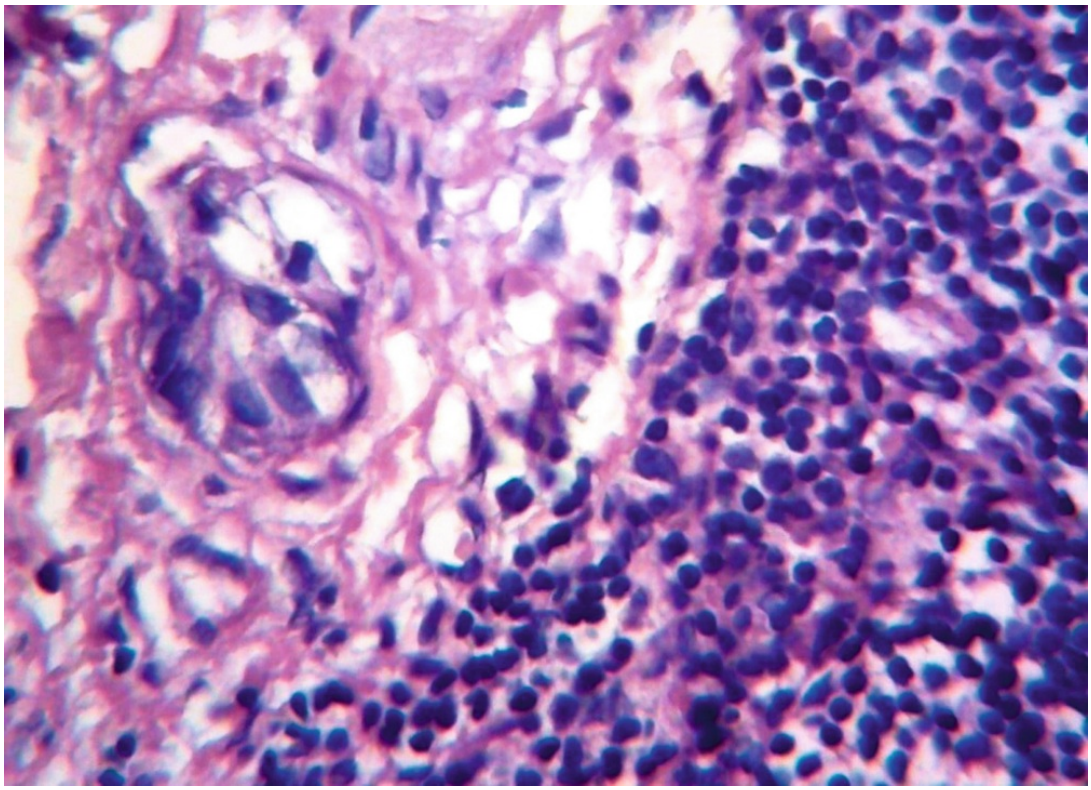

Fig. 2.29 Metastatic emboli in the capsule vessels of the lymph node. Vessel diameters reach 28 and 49 μm. Hematoxylin and eosin stain

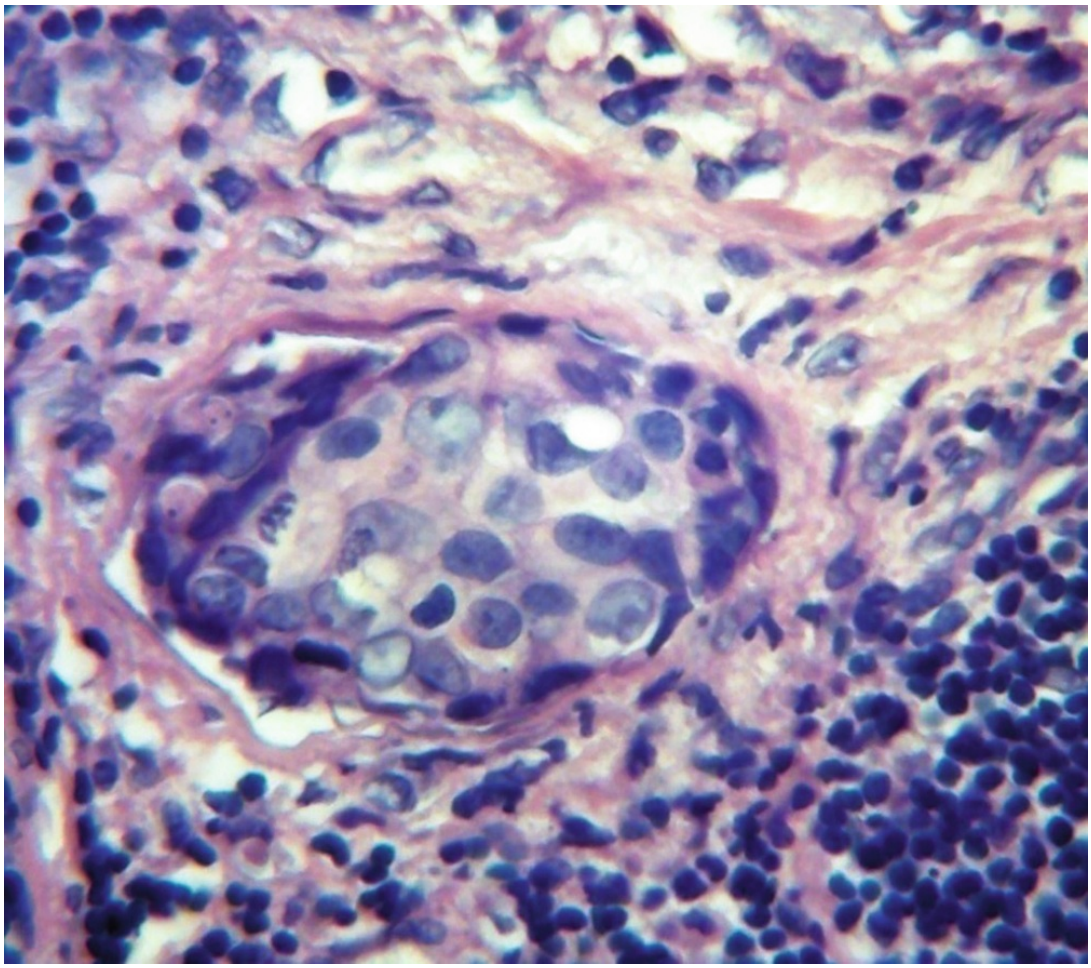

Fig. 2.30 Lymph node. Cancer emboli in lymphatic vessels in breast cancer. Hematoxylin and eosin stain

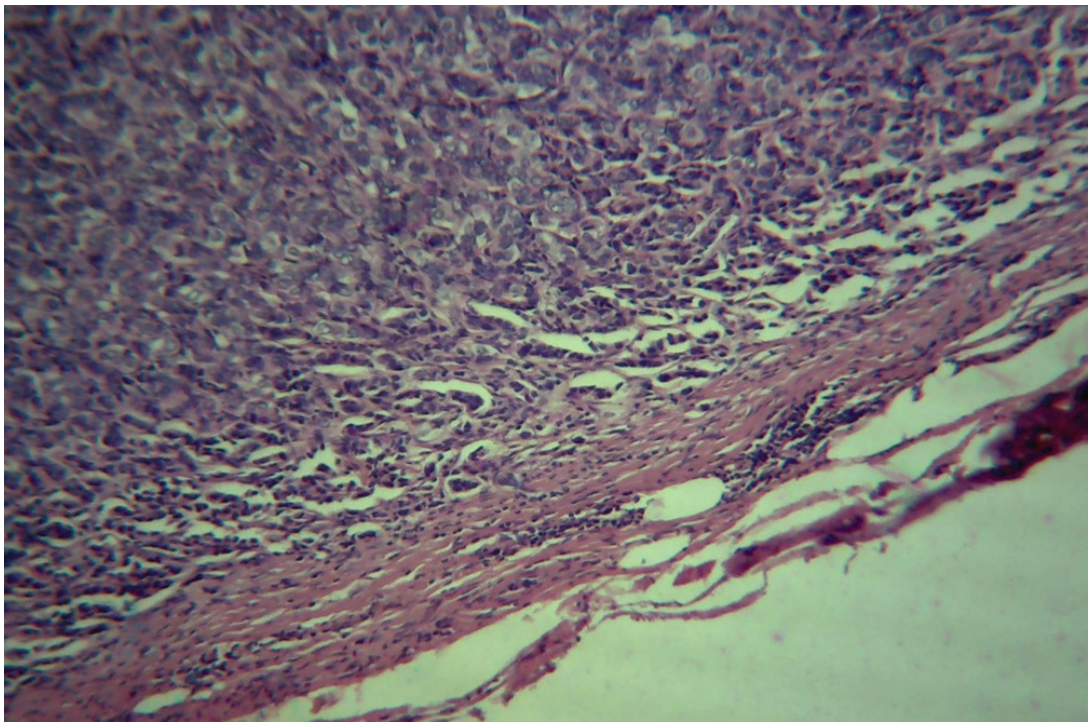

Fig. 2.31 Breast cancer with metastases in axillary lymph nodes. The lymph node affected by metastatic disease is visible. Hematoxylin and eosin stain

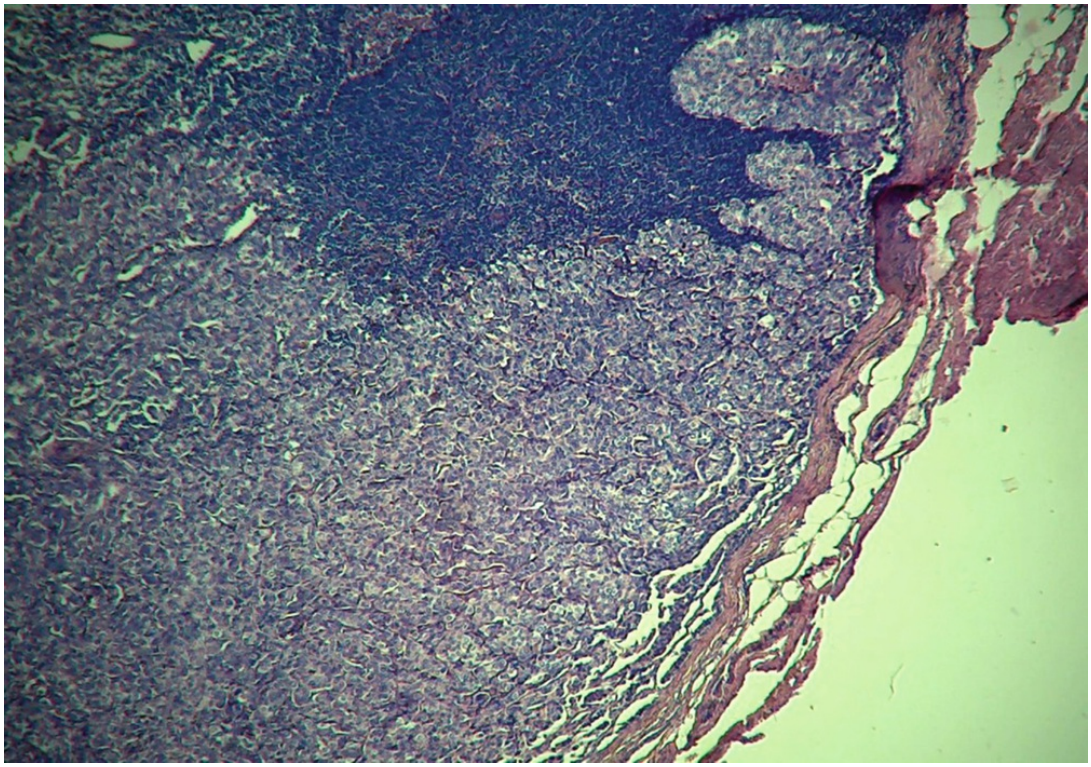

Fig. 2.32 Subtotal metastatic lesion of the lymph node in breast cancer. Hematoxylin and eosin stain

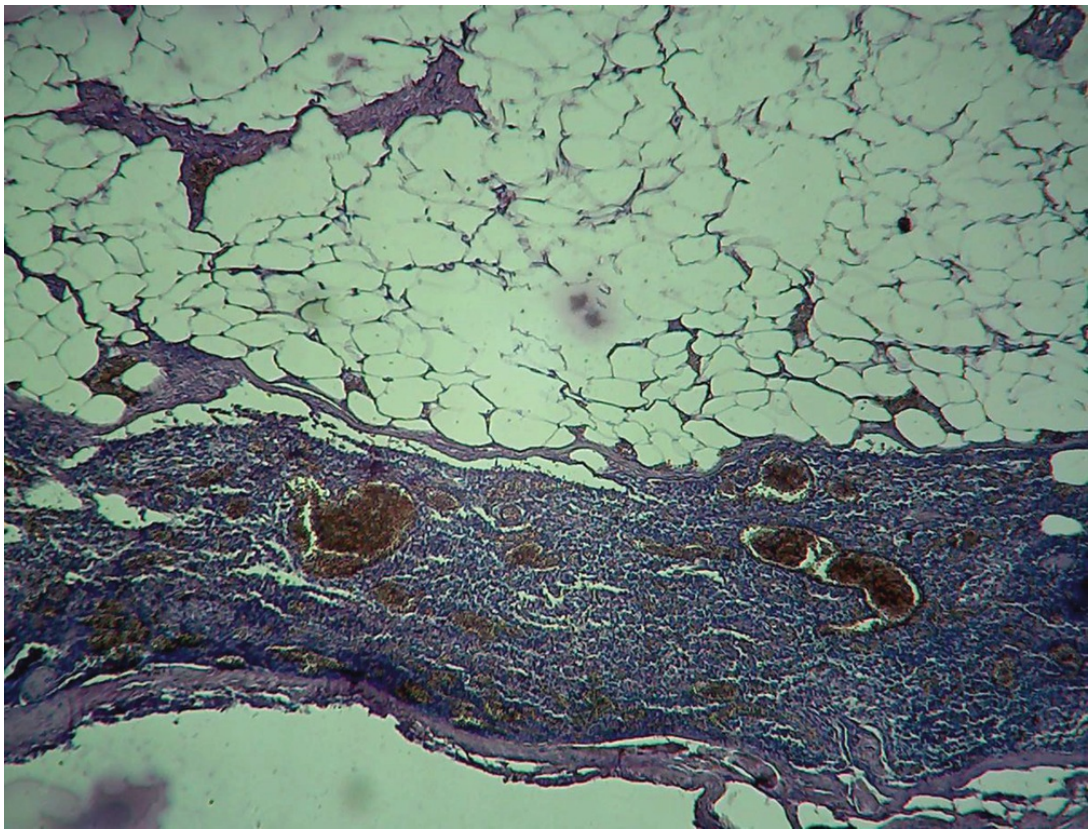

Fig. 2.33 Adipose involution of the lymph node. Hematoxylin and eosin stain

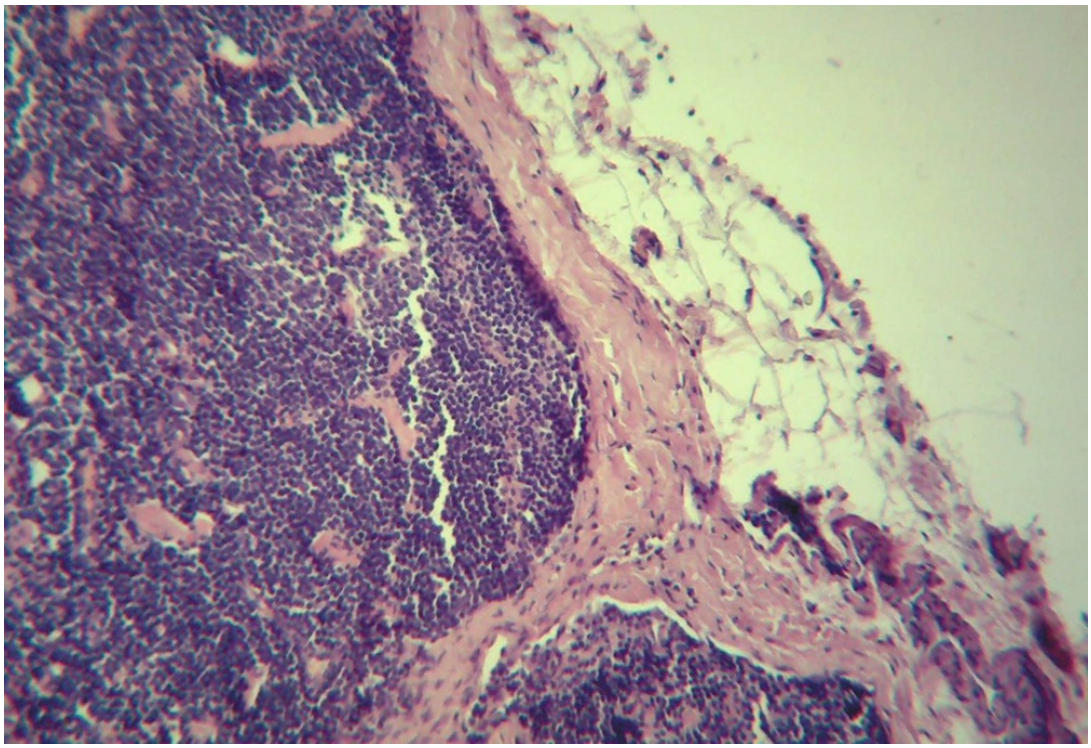

Fig. 2.34 Branches of the lymph node capsule extending into the interior and dividing the nodes into lobules. Hematoxylin and eosin stain

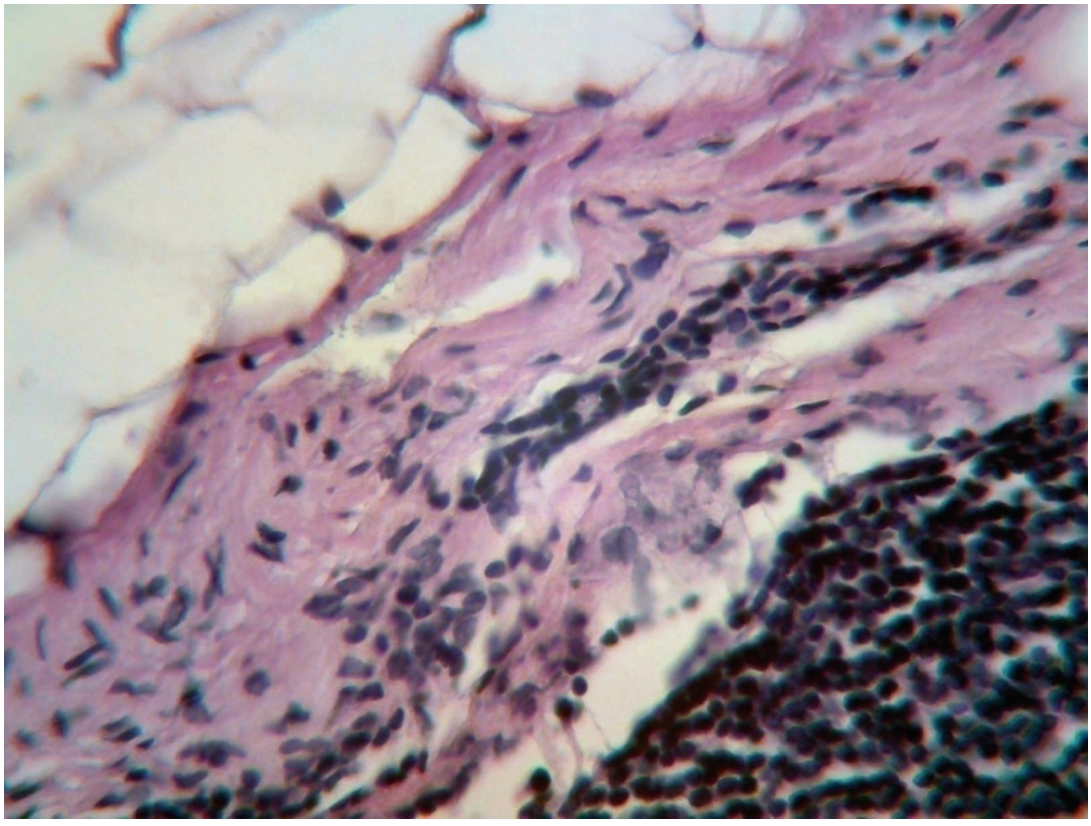

Fig. 2.35 The lymph node capsule with lymphatic vessels. Hematoxylin and eosin stain

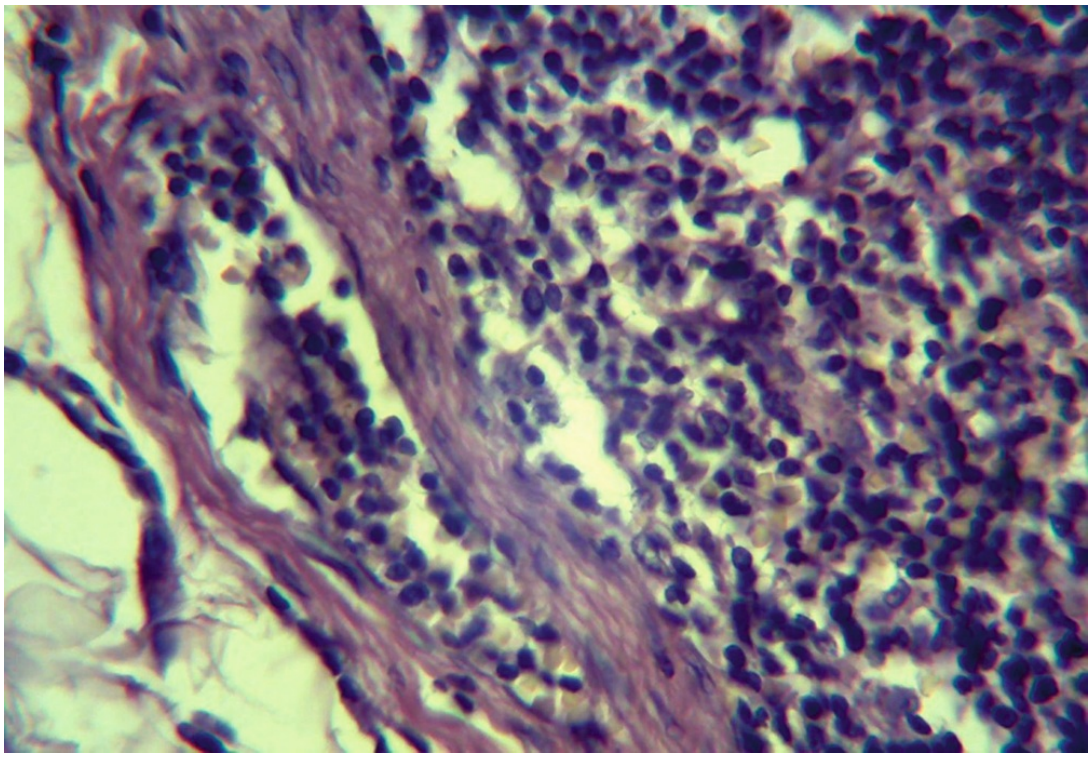

Fig. 2.36 The lymph node capsule with lymphatic vessel passing through it; it is filled with lymphocytes. Hematoxylin and eosin stain

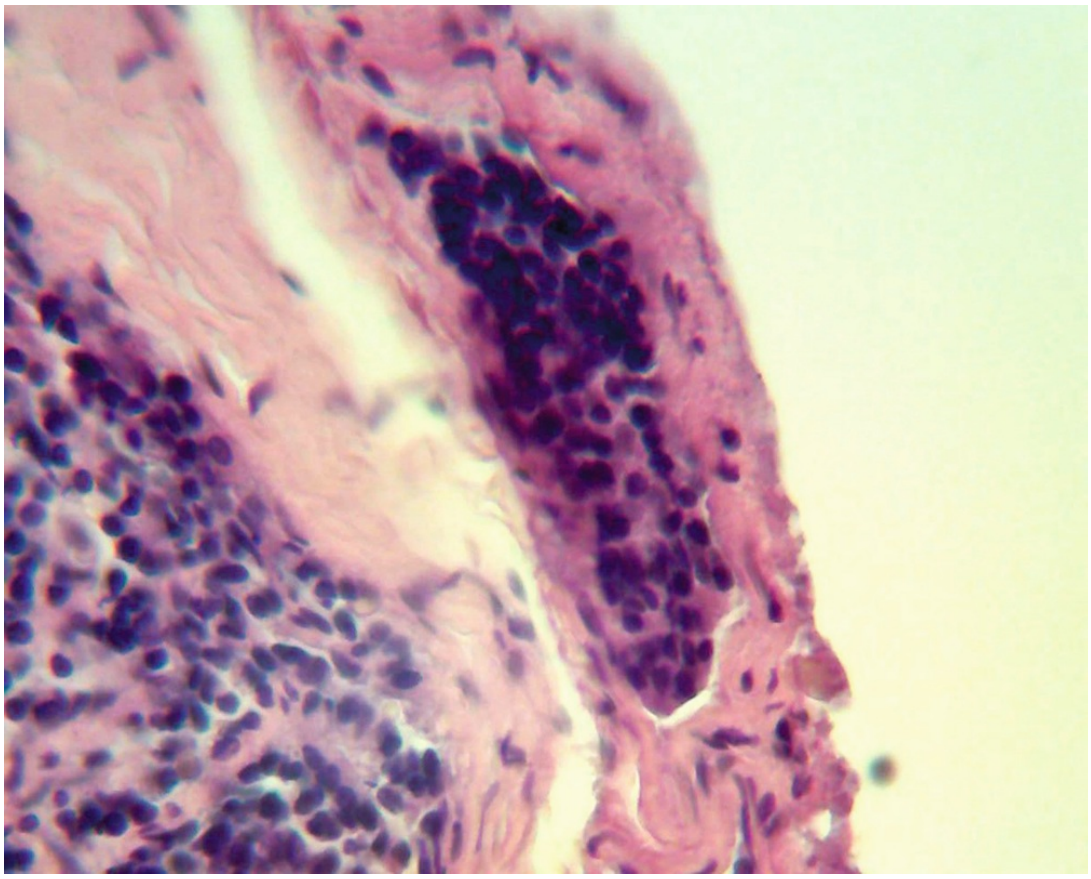

Fig. 2.37 The lymph node capsule and intracapsular vessels; lymphocyte aggregates are seen in the lumen. Hematoxylin and eosin stain

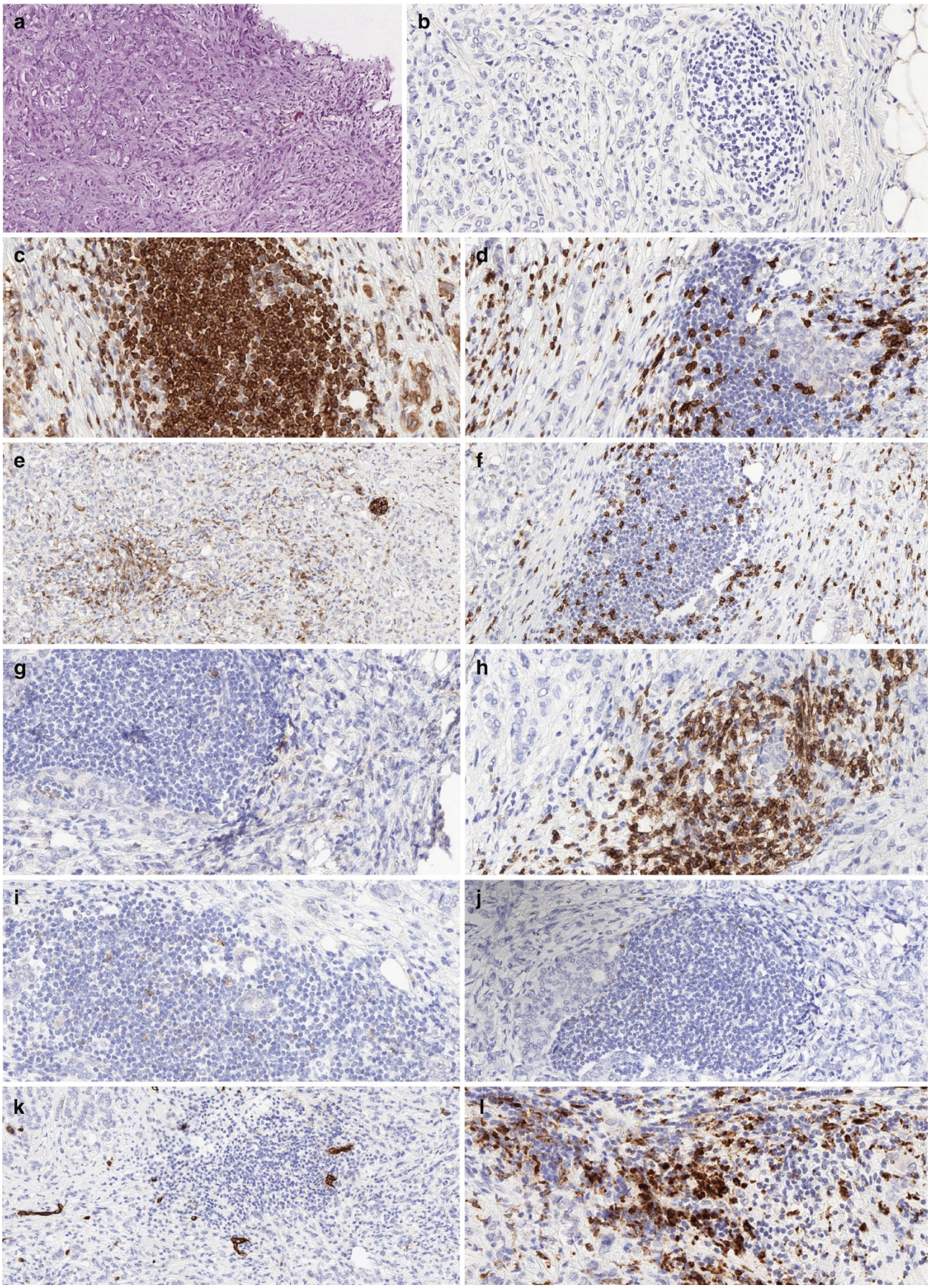
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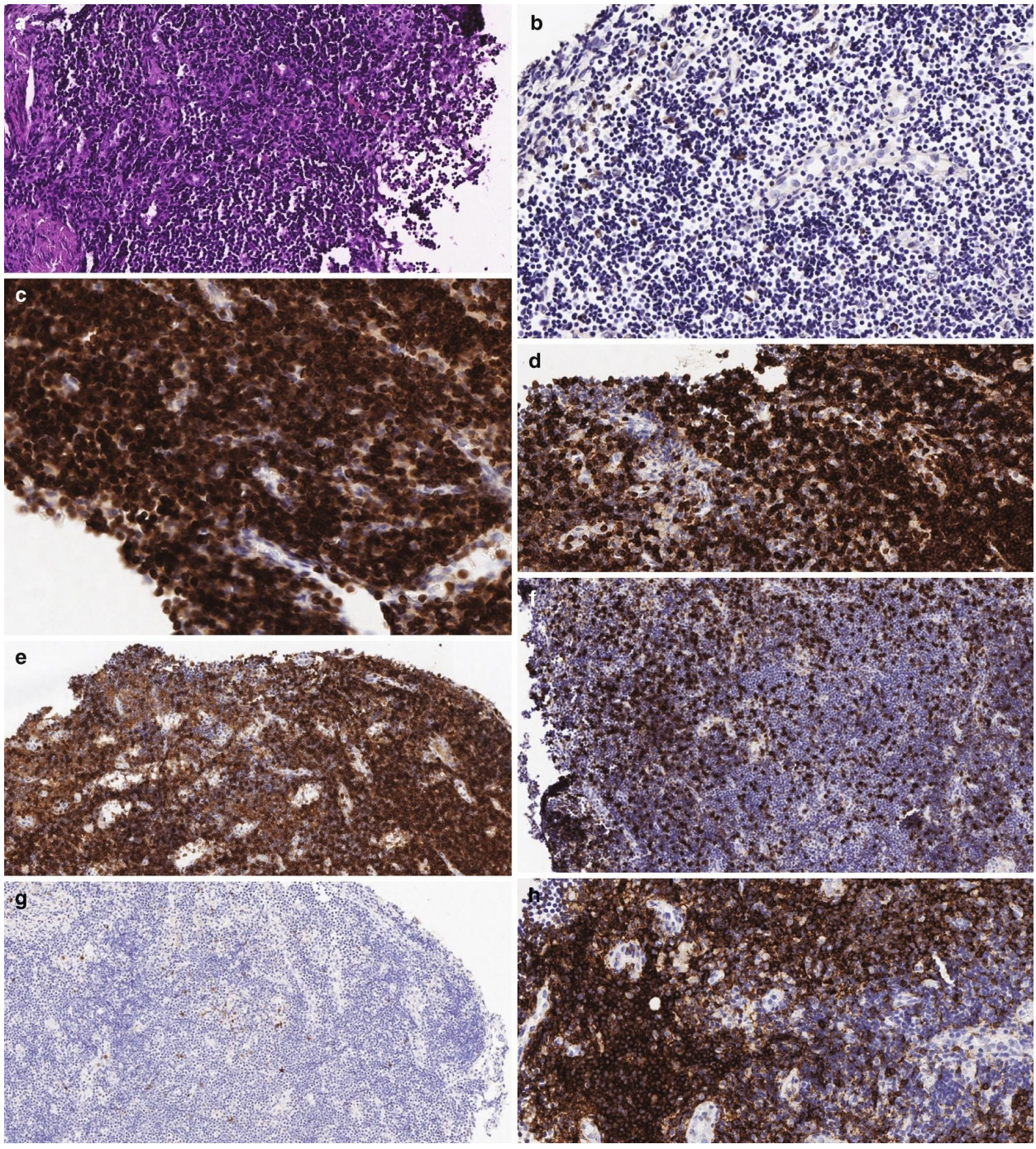
Fig. 2.38 Primary sentinel lymph node. The lymph node is subtotally replaced by a low-grade malignant tumor that forms solid structures and consists of polymorphic cells with hyperchromic nuclei; a large number of mitotic figures are noted. The tumor spreads to the paranodal fatty tissue. Small areas of lymphoid tissue. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34 (QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain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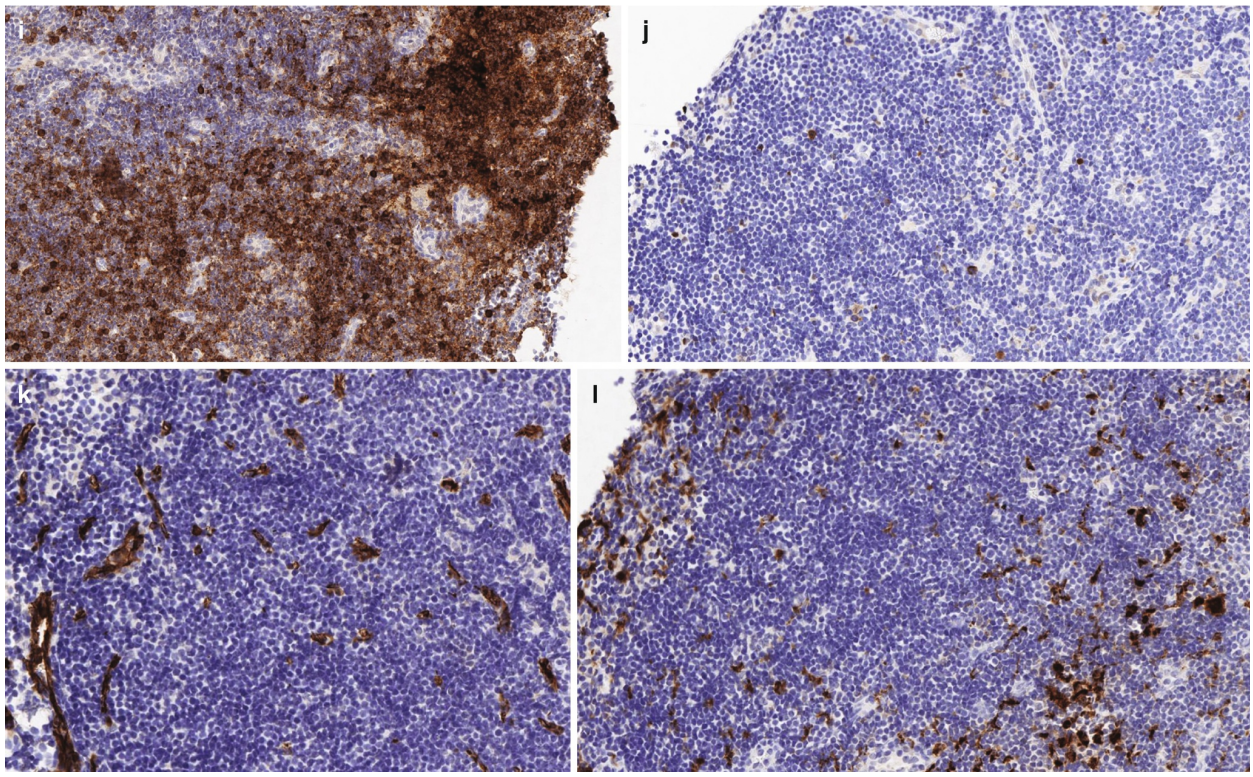
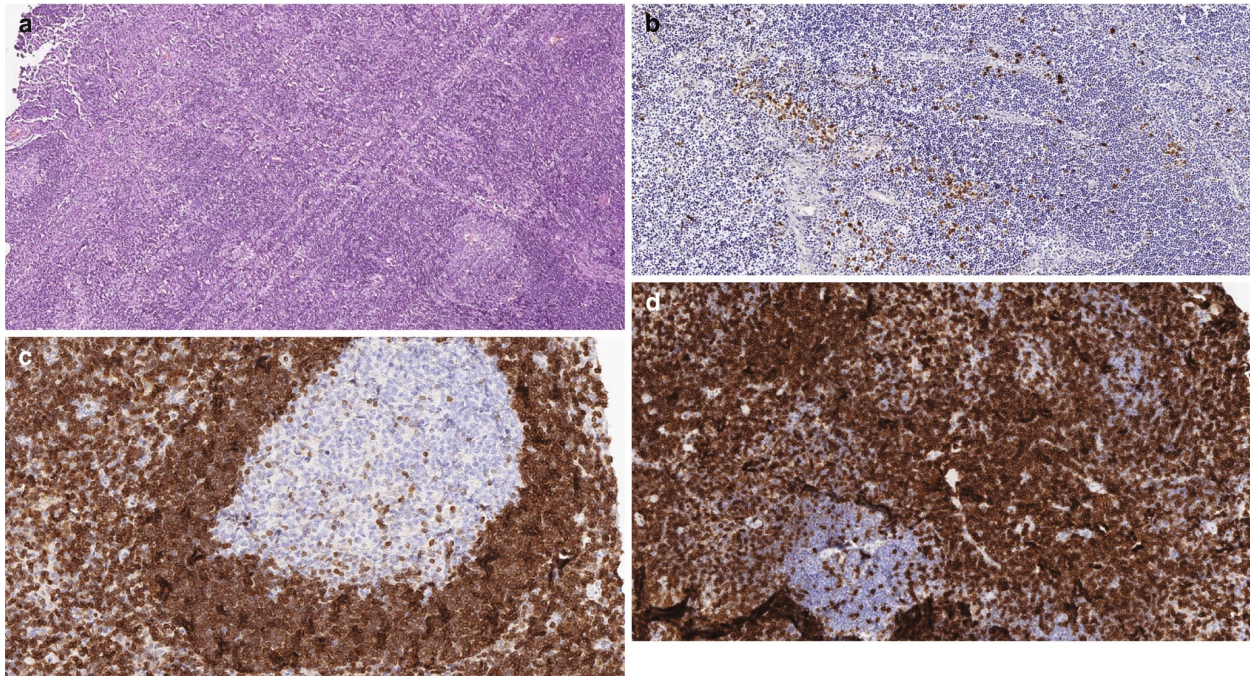


Fig. 2.39 Secondary sentinel lymph node. The capsule is thin; the sinuses, both marginal and internal, are open and contain histiocytes with an admixture of lymphocytes. Lymphoid follicles with germinal centers of different sizes. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34 (QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain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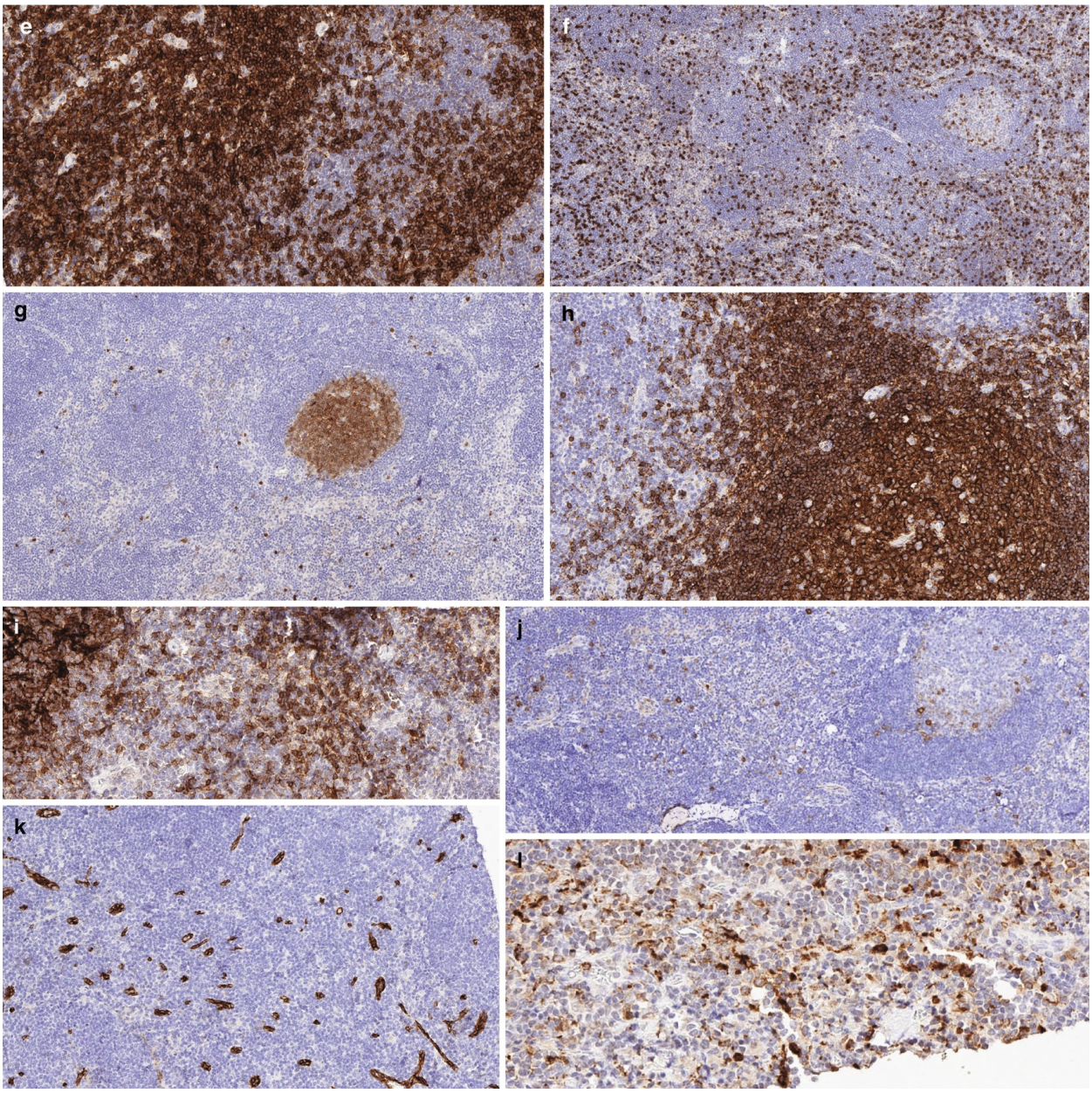
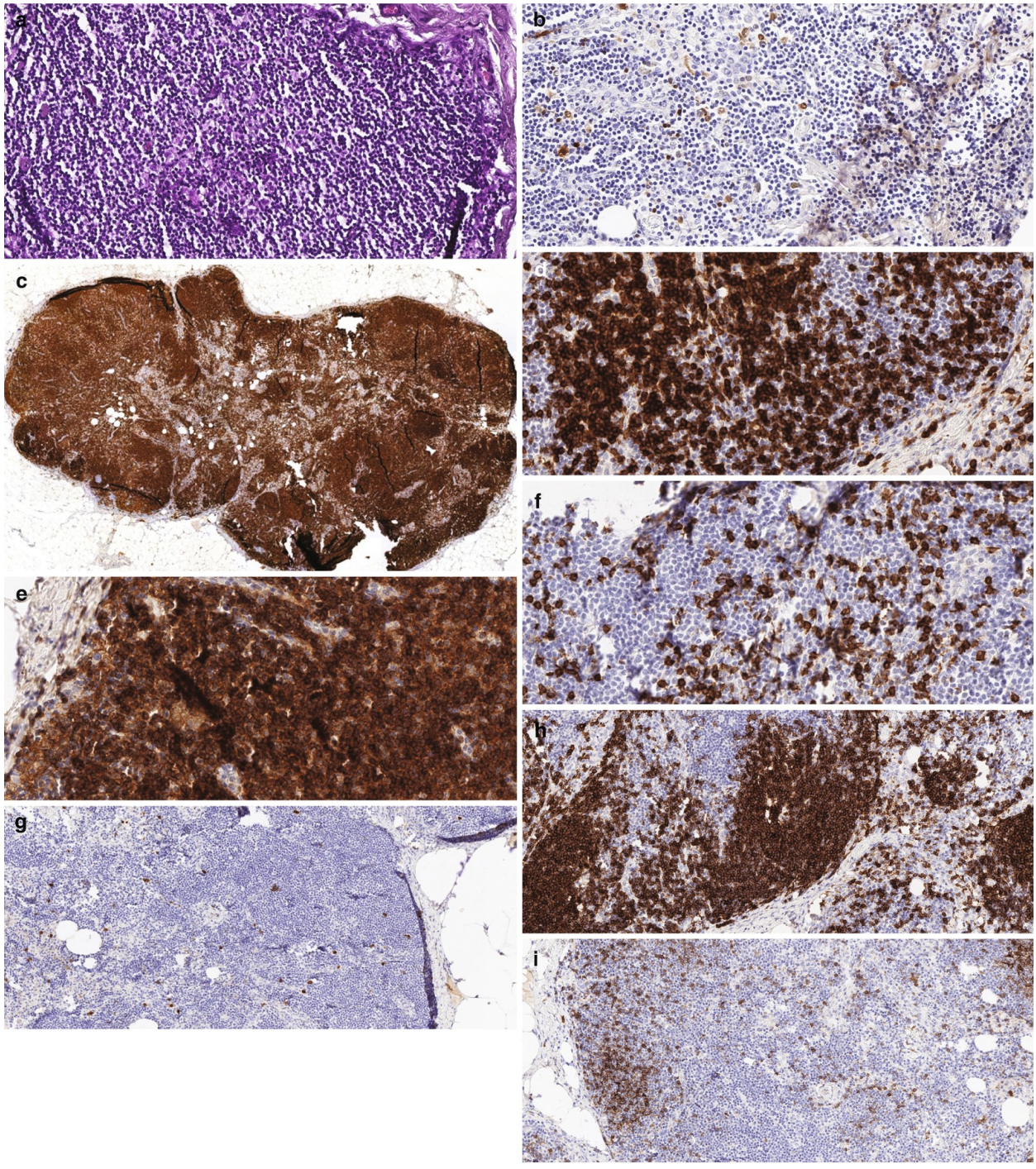


Fig. 2.40 The lymph node in cancer is clinically without metastases. The capsule is thin and of uneven thickness; marginal and internal sinuses contain histiocytes with a large admixture of lymphocytes. In all areas of the lymph node visible lymphoid follicles with germinal centers of different sizes are identified, expansion of paracortex is moderately expressed. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34

(QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain



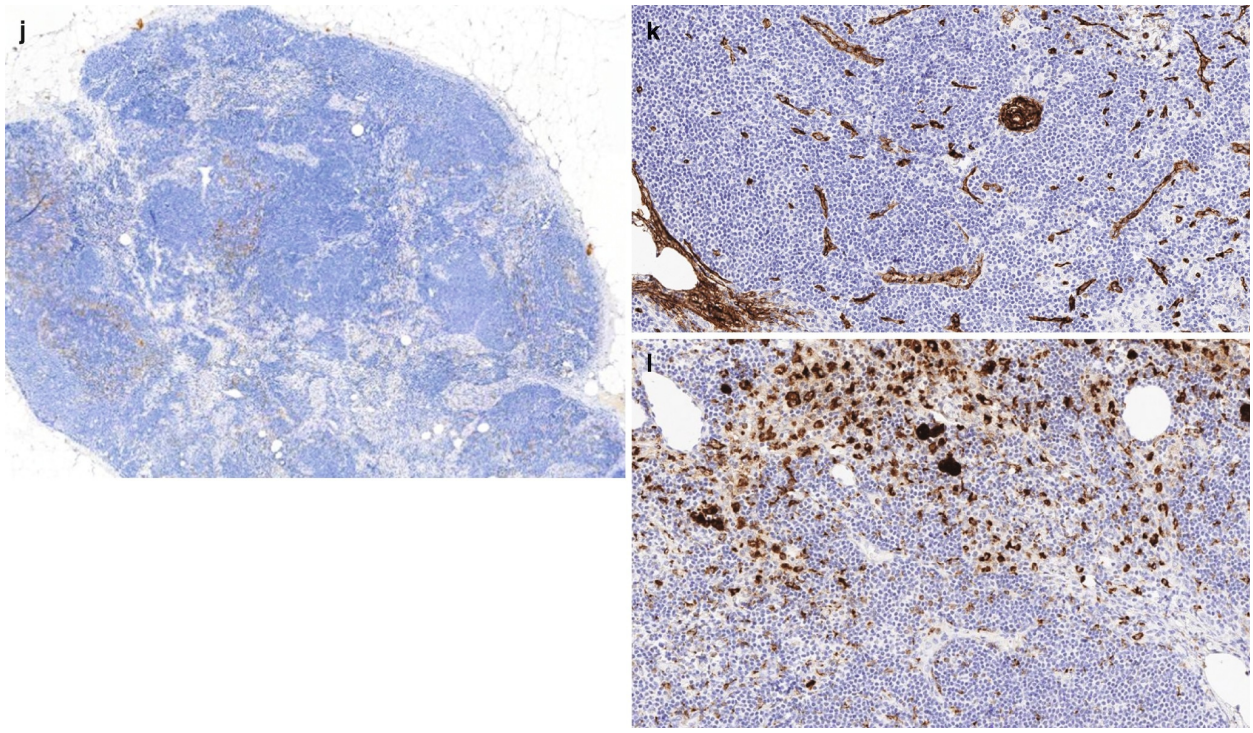


Fig. 2.41 The lymph node in cancer is clinically without metastases. Extranodal adipose tissue does not contain lymphocytes. The capsule is thin and uneven in thickness. Small single clusters of histiocytes are determined. Mainly in the paracortical region of the lymph node, large lymphoid follicles with terminal centers of different sizes are determined. A moderate expansion of paracortex is also noted. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34 (QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain

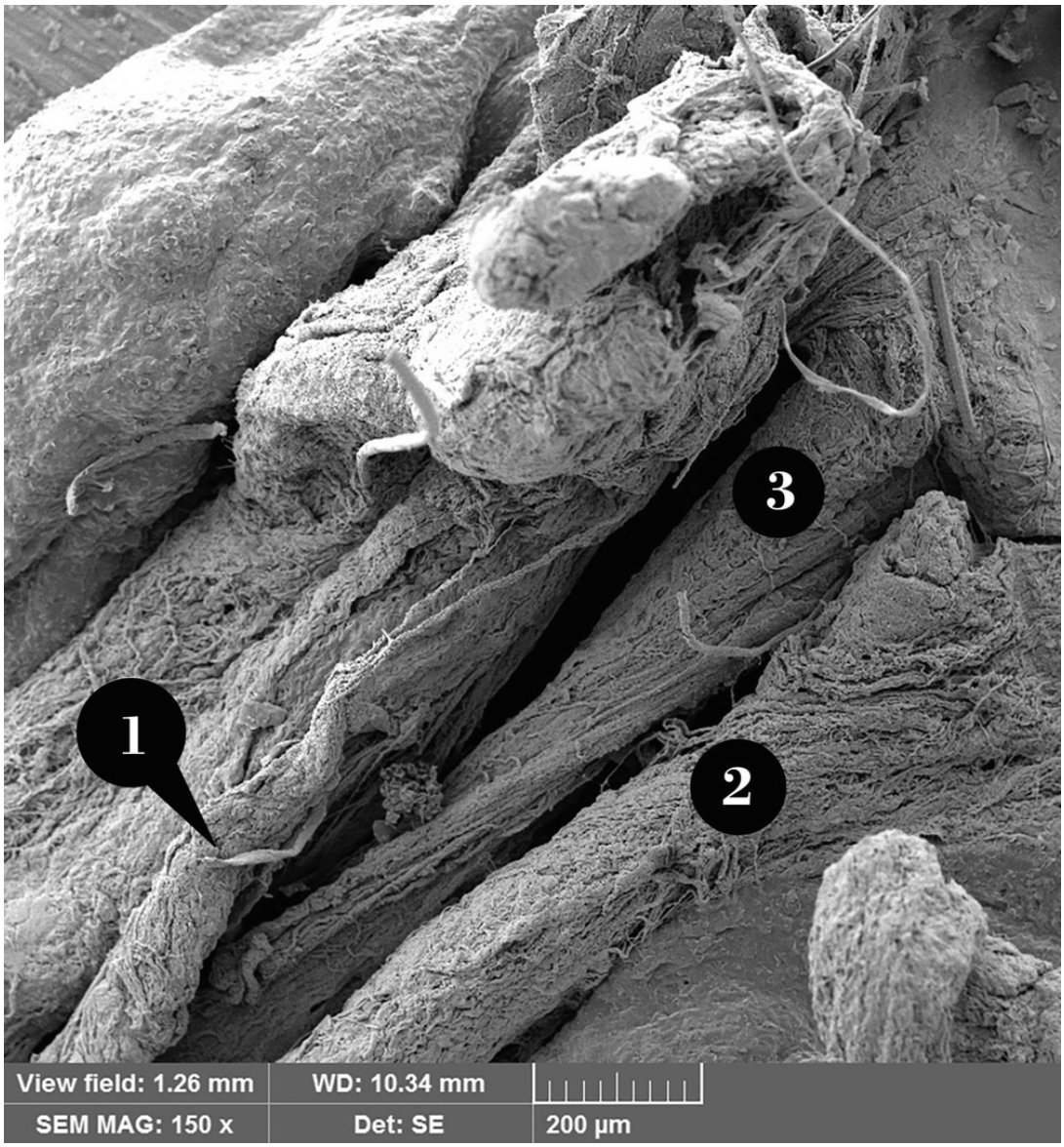


Fig. 2.42 Electron microscopy of the lymph node capsule with vessels penetrating into its thickness (1, 2, 3)

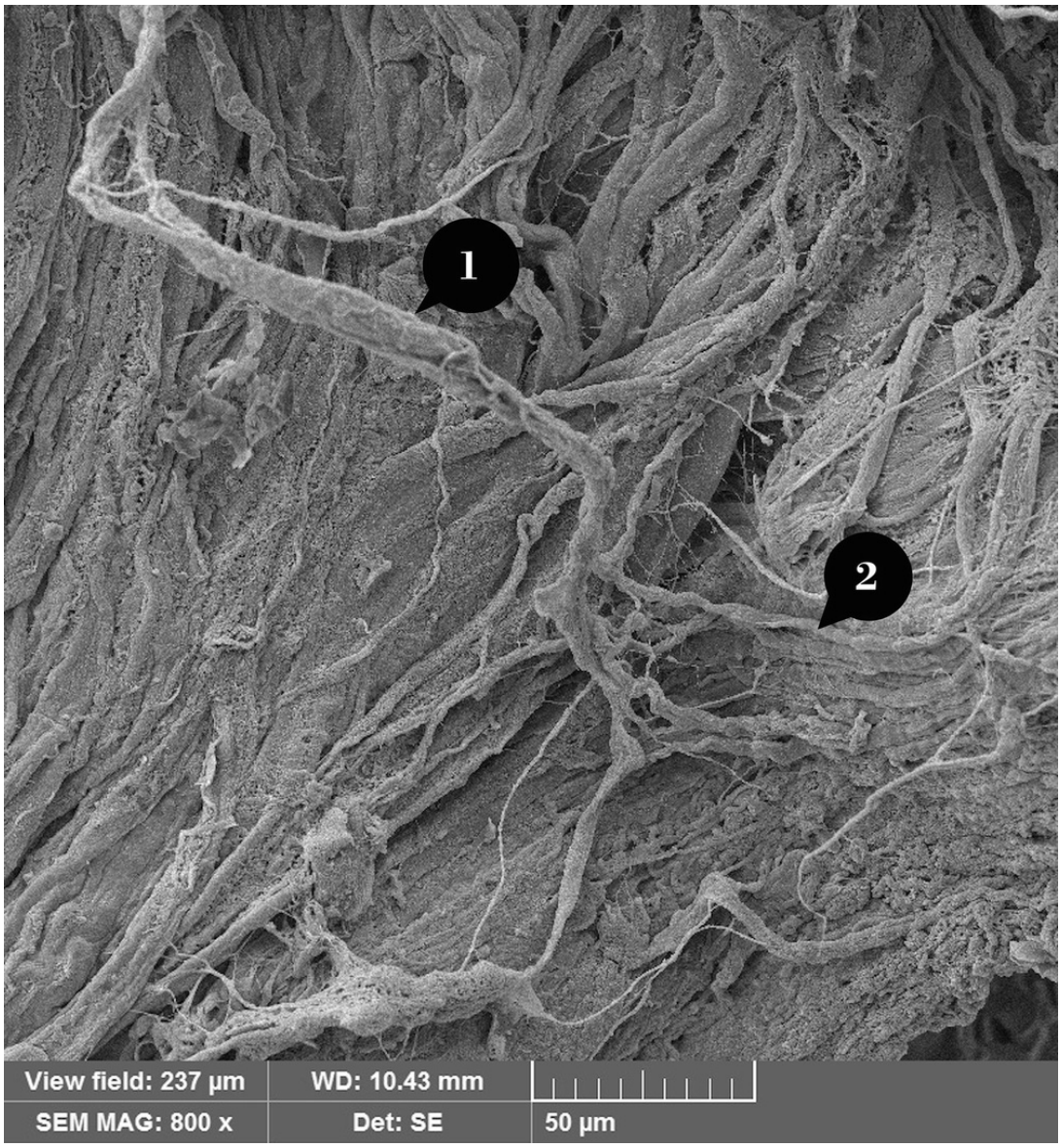


Fig. 2.43 Electron microscopy of the lymph node capsule. Against the connective tissue fibers, there are a lymphatic capillary and the smallest vessels that provide trans-tissue exchange. There is a vascular distention with cistern formation

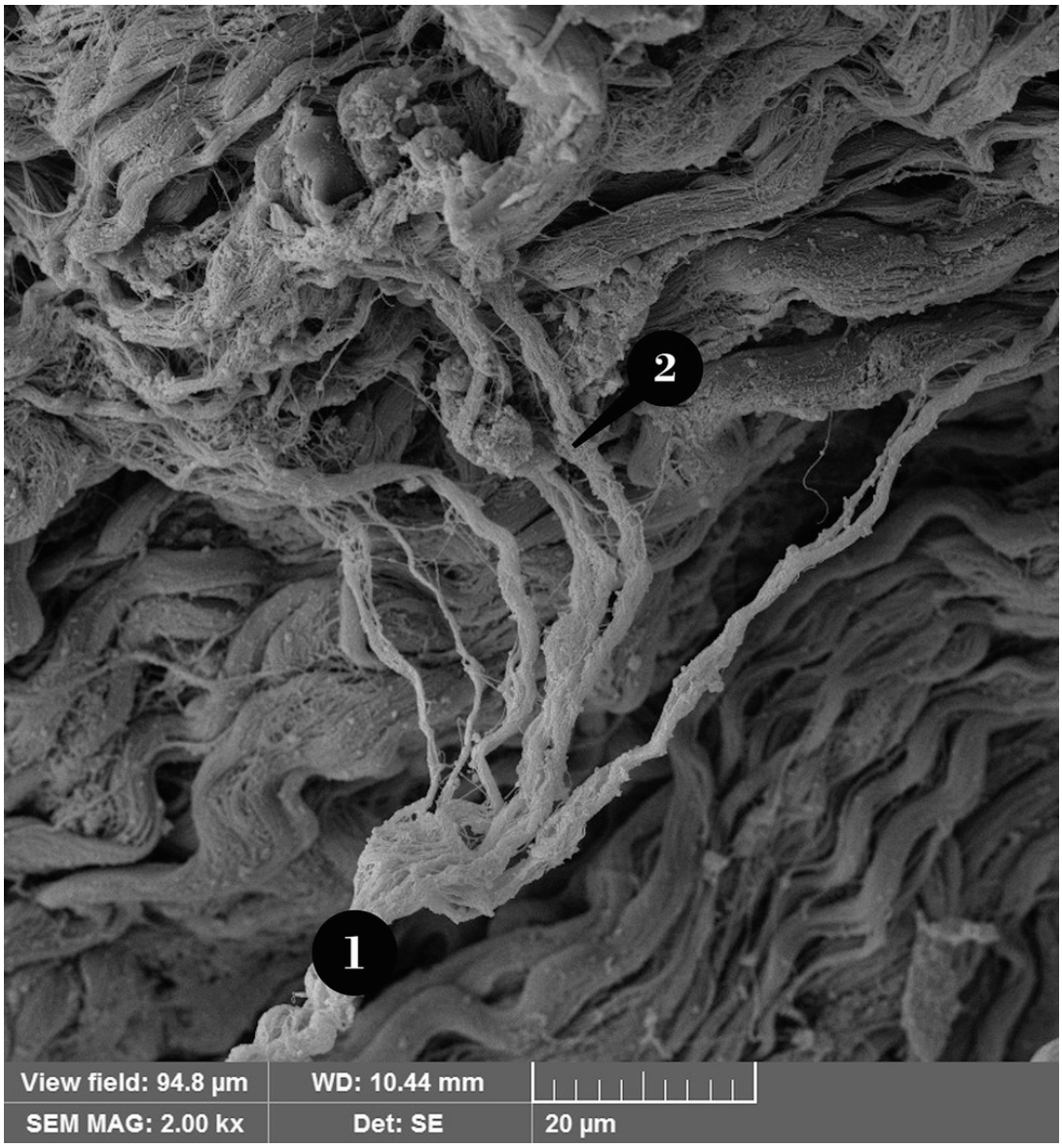


Fig. 2.44 Electron microscopy. The lymph node capsule. There is a lymphatic vessel (2) in the thickness of the connective tissue and many small branches (2) forming the smallest plexus

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3. Lymphatic Mapping in Cancer

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Keywords Lymphatic system – Axillary lymphatic apparatus – Breast cancer – Lymphatic map – Lymph flow

The opportunity to see the state of the regional lymphatic collector with distribution centers of lymph flow and differentiation of immune system cells is an extremely important factor for the personification of treatment guidelines for oncology diseases. It is extremely difficult to predict the lymph movement logistics, both in vivo and ex vivo, on the basis of mechanical dissection of the regional lymphatic apparatus in cancer. Improvement of the research effectiveness can only be achieved on the basis of color lymphography and a number of other more complex research.

The lymphatic mapping modeled ex vivo with the help of supersonic generator can clearly show the direction of lymph flow

and assess macroscopic state of the sentinel lymph node, angiogenesis intensity, and other parameters. Based on our experience, it can be assumed that the lymphatic mapping is the most important basis for patient's prognosis and prospects, since these data demonstrate the dynamic processes of the regional lymphatic zone. When analyzing lymphatic mapping, there is the possibility of detailed and selective morphological examination of microcirculation vessels, lymph nodes, and other stroma components. It can be assumed that the lymphatic mapping in cancer is the "gold" standard for assessing the state of lymphatic collectors in oncology diseases.

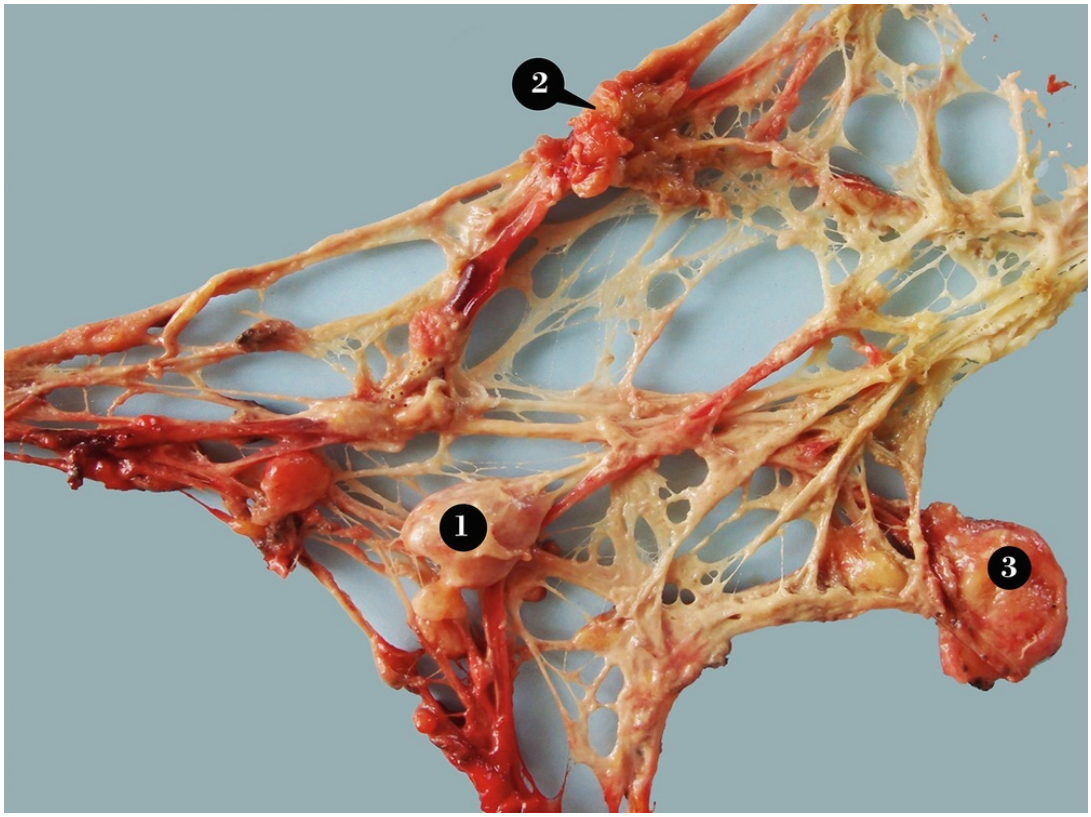

Fig. 3.1 Lymphatic mapping of the axillary region in breast cancer. There are the main lymphatic drainage basins. The stromal component is moderately expressed. Neo-lymphangiogenesis is active in the 2 node area. This node is deformed and scarred. The 1 and 3 lymph nodes do not have such gross changes

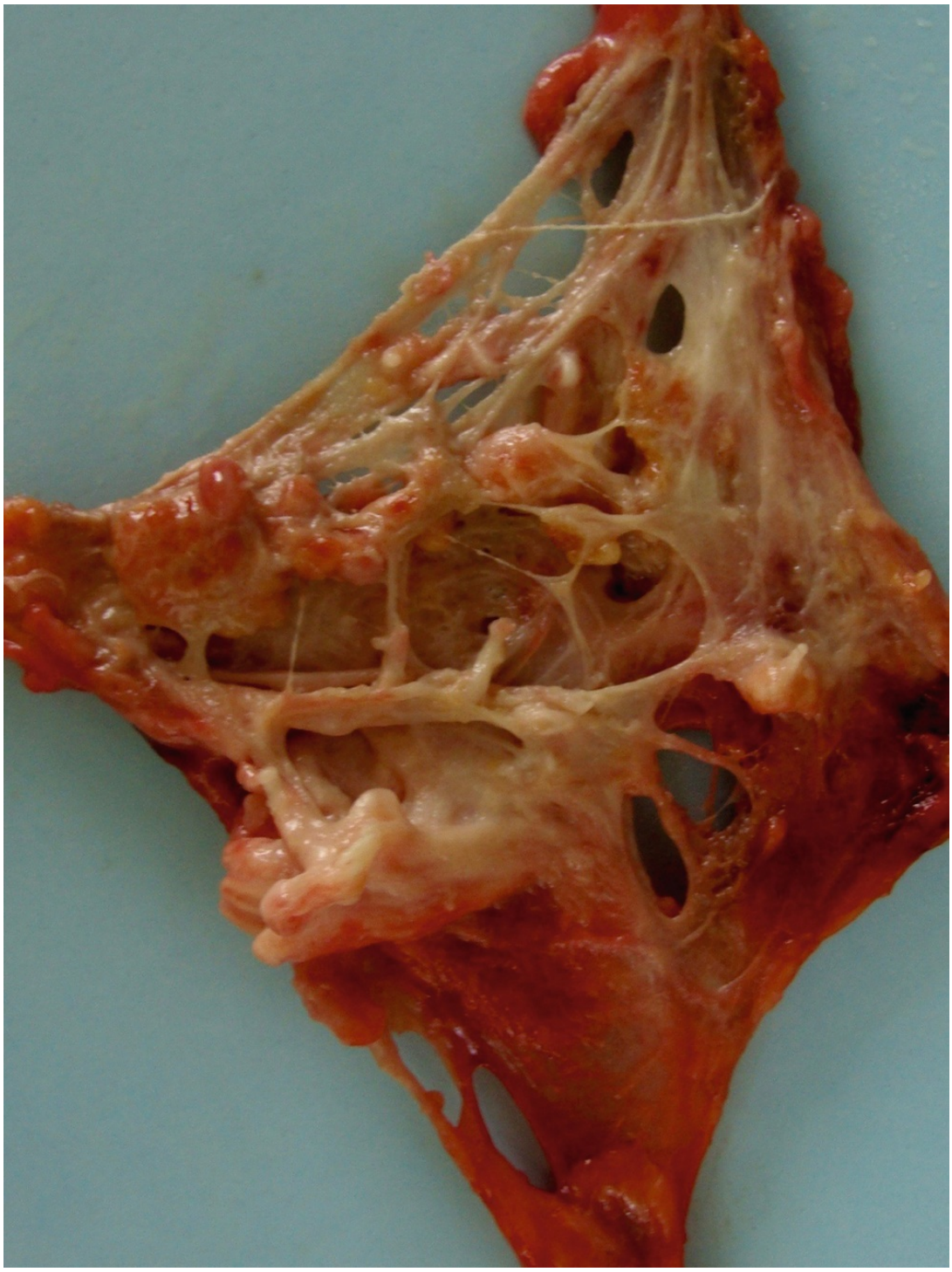

Fig. 3.2 Stage of lymphatic dissection. An adipose tissue is removed from a portion of specimen; large vessels and lymph nodes are visible. The stromal component is significantly expressed

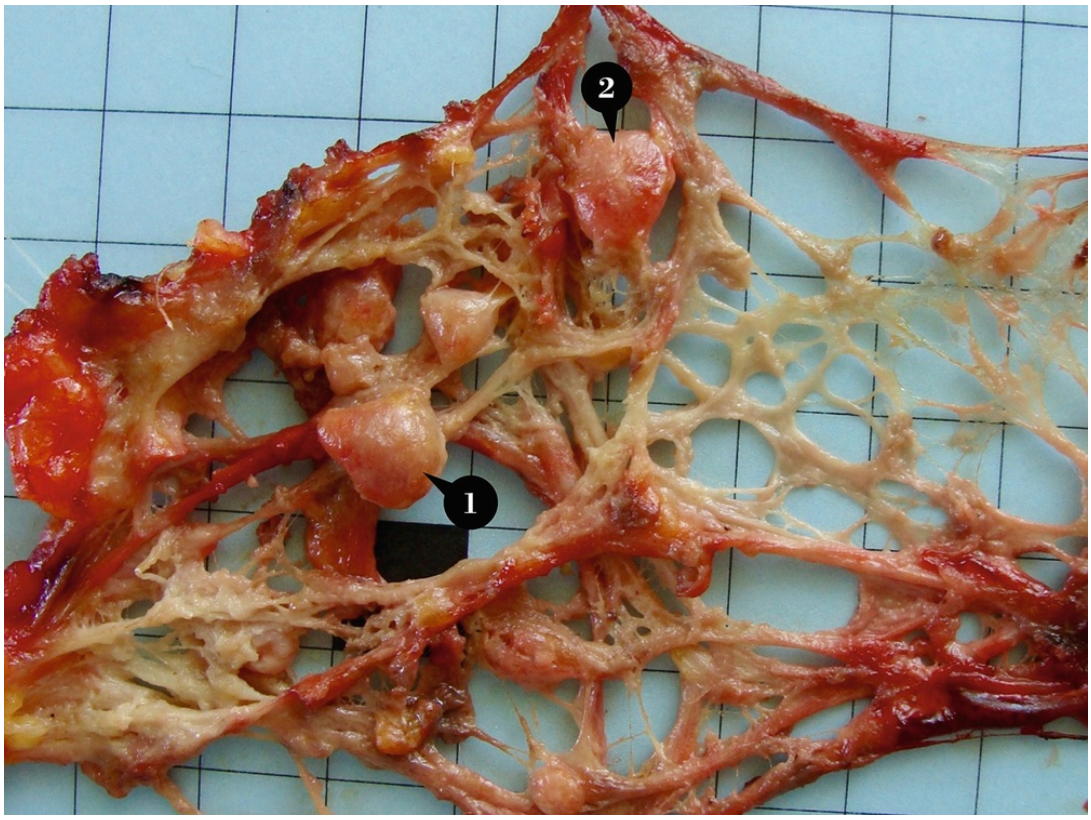

Fig. 3.3 Lymphatic mapping of the axillary drainage system in breast cancer. The lymph nodes (1, 2) are enlarged and reach 10 mm; their capsule is practically unchanged. Perinodular angiogenesis is not active. There is a massive network of lymphatic collaterals and anastomoses with a large diameter of the vessels (1–1.5 mm) outside the lymph nodes

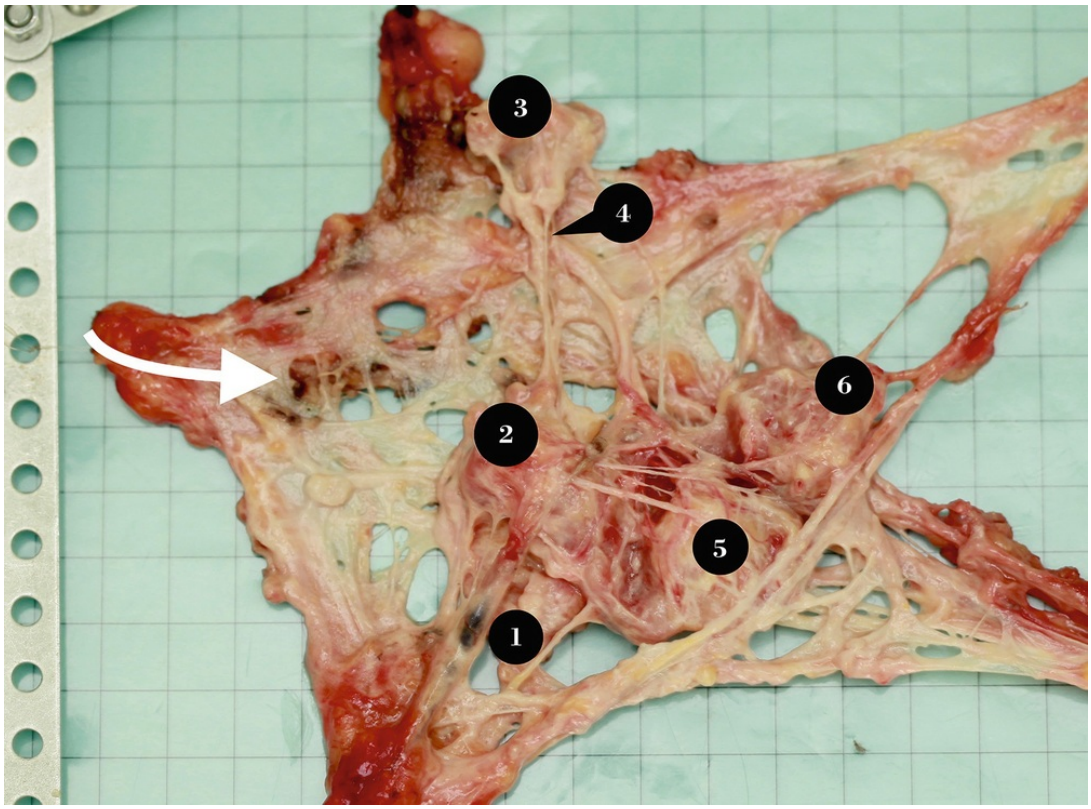

Fig. 3.4 The full-scale lymphatic mapping of the axillary region in stage III breast cancer. The arrow indicates the lymph movement. Figure 2 illustrates the sentinel lymph node and 4, 5, 6 illustrate nodes of the following arrangements determining metastasis zonality. The vessels of this lymph node group are well expressed (1.3). The stroma is preserved

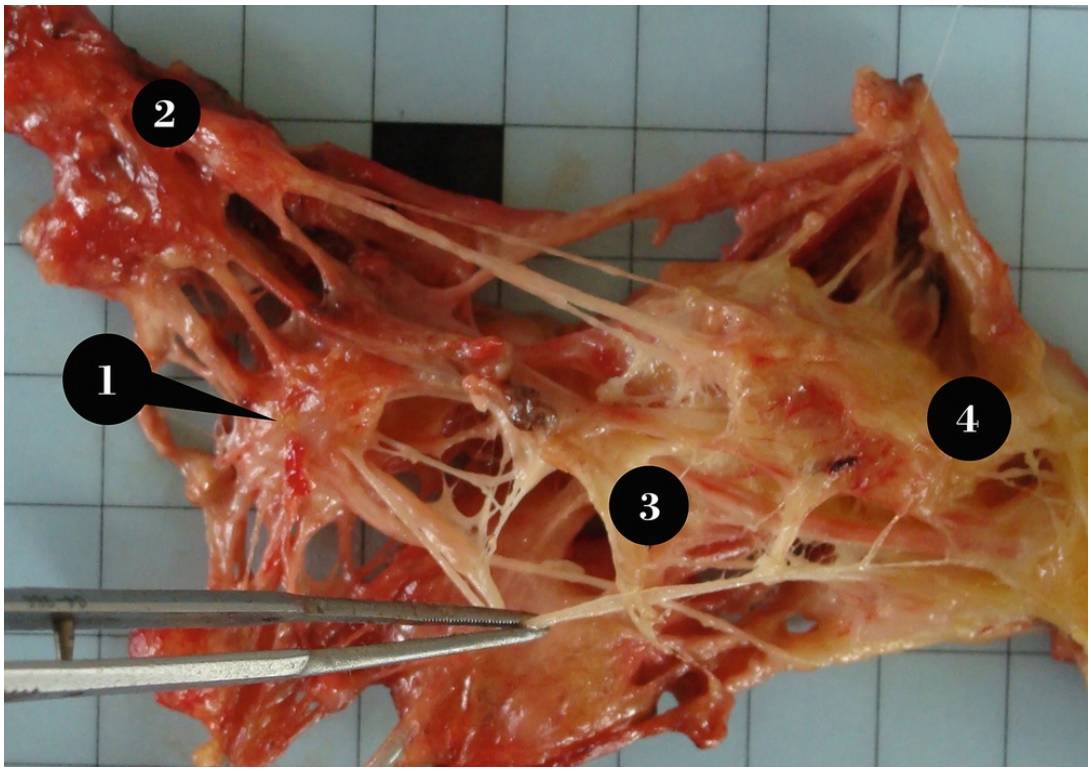

Fig. 3.5 Lymphatic mapping of the axillary region in stage III breast cancer. There are many visible enlarged lymph nodes (1,2,4). The 2 node is the nearest to the tumor; its size is about 10 mm. The 4 node is the largest one. Its length is about 35 mm, it is surrounded by a large number of lymphatic vessels (3), and stroma is expressed. The 2 lymph node is susceptible to the most profound changes: it is wrinkled and changed due to scarring; the number of lymphatic vessels flowing into the node is in large excess over the norm

Fig. 3.6 Lymphatic mapping of the axillary region in breast cancer. There is an enlargement of the lymph nodes in all levels. Nodes' size reaches 20–30 mm. The stromal component is moderately expressed. Neo-lymphangiogenesis is not active

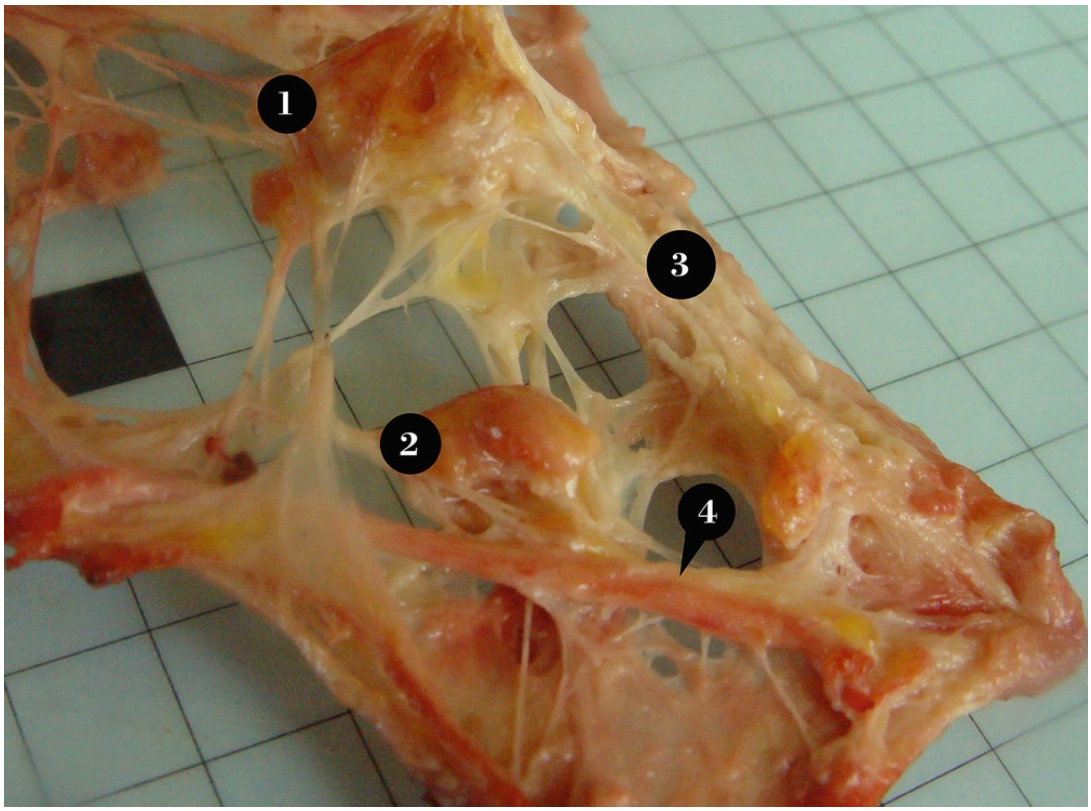

Fig. 3.7 The fragment of lymphatic mapping of the axillary region in breast cancer. Figures 1 and 2 illustrate the enlarged lymph nodes and 3 and 4 – vascular trunks of the great vessel type. After ultrasonic dissection, stroma is partially preserved

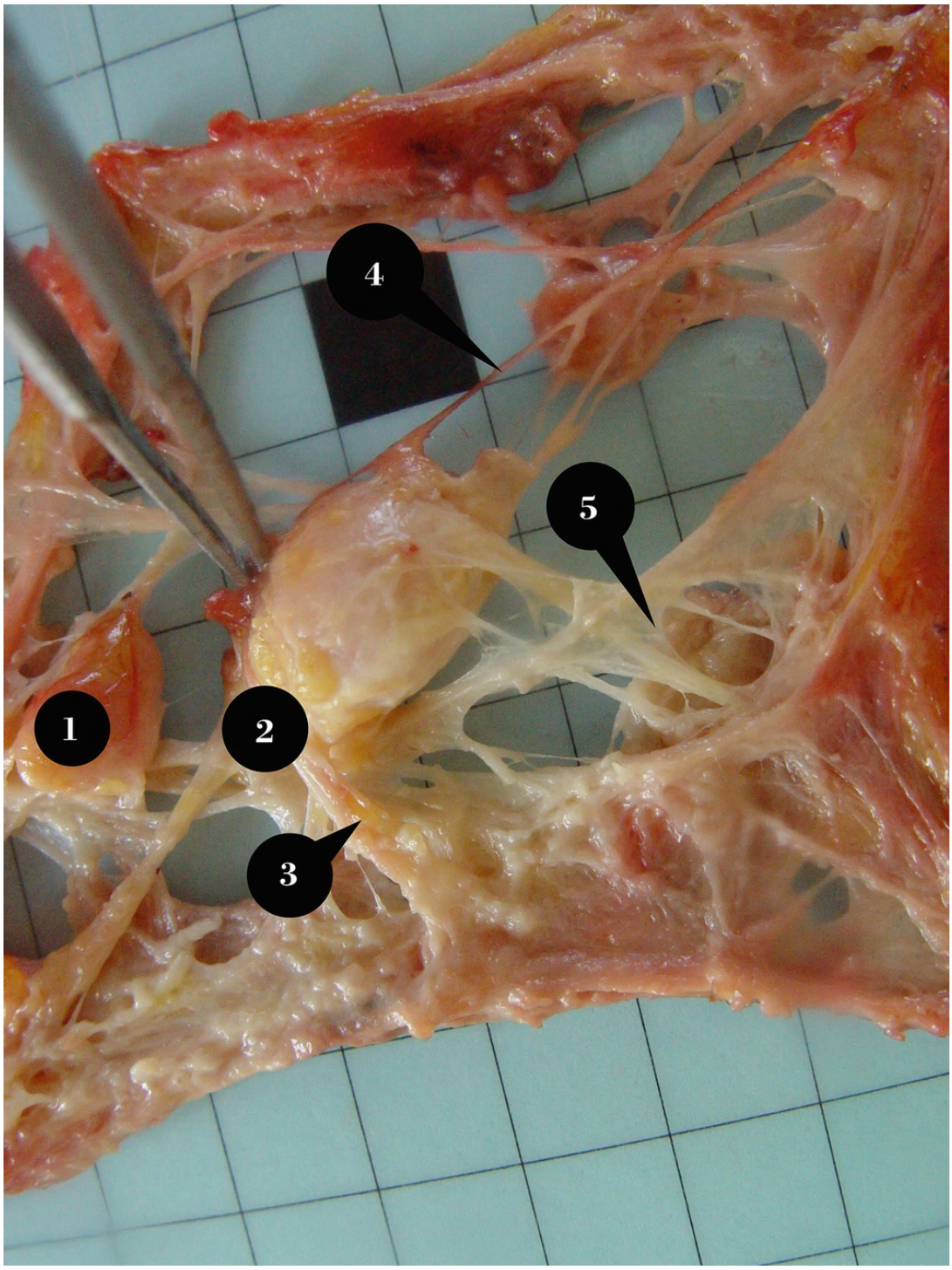

Fig. 3.8 The fragment of lymphatic mapping of the axillary region after careful removal of adipose tissue. All elements of the lymphatic system are distinguished: lymph nodes (1,2) and lymphatic vessels (3,4,5). The lymph node capsule is filled with adipose tissue

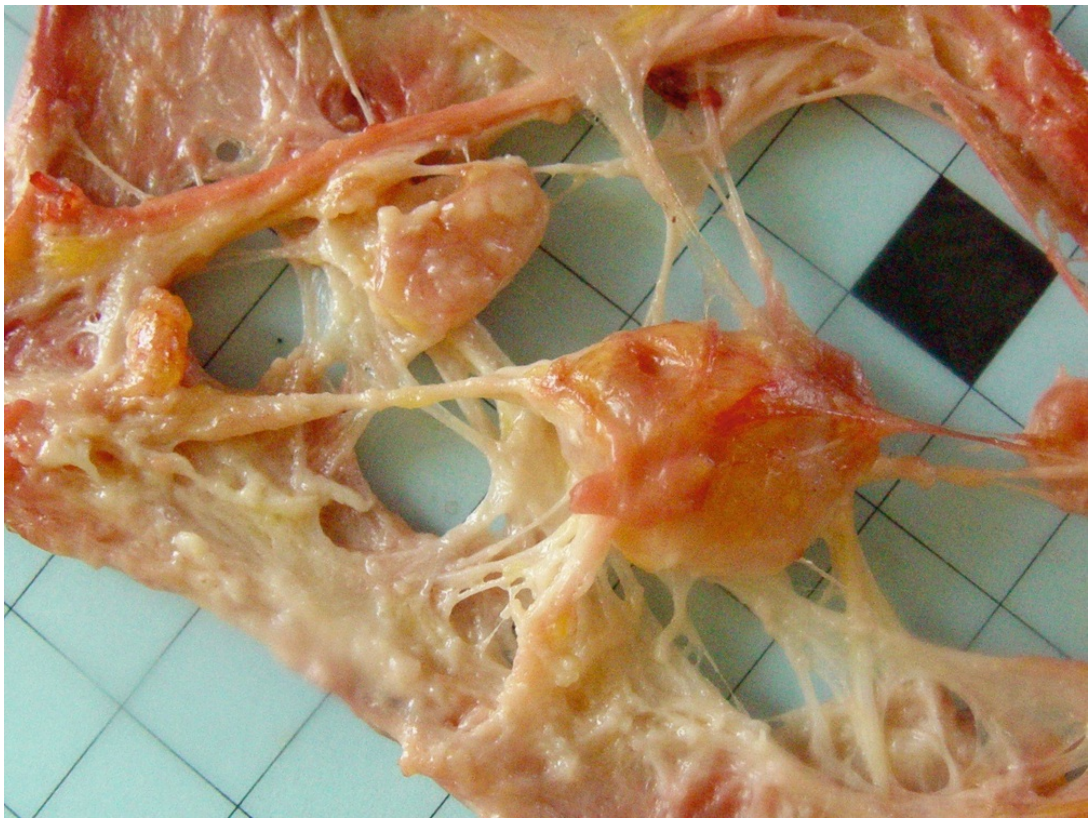

Fig. 3.9 The proximal part of lymphatic mapping. There is a sentinel lymph node with active neo-lymphangiogenesis. The node capsule has significant abnormalities; its surface is tuberous, with retractions

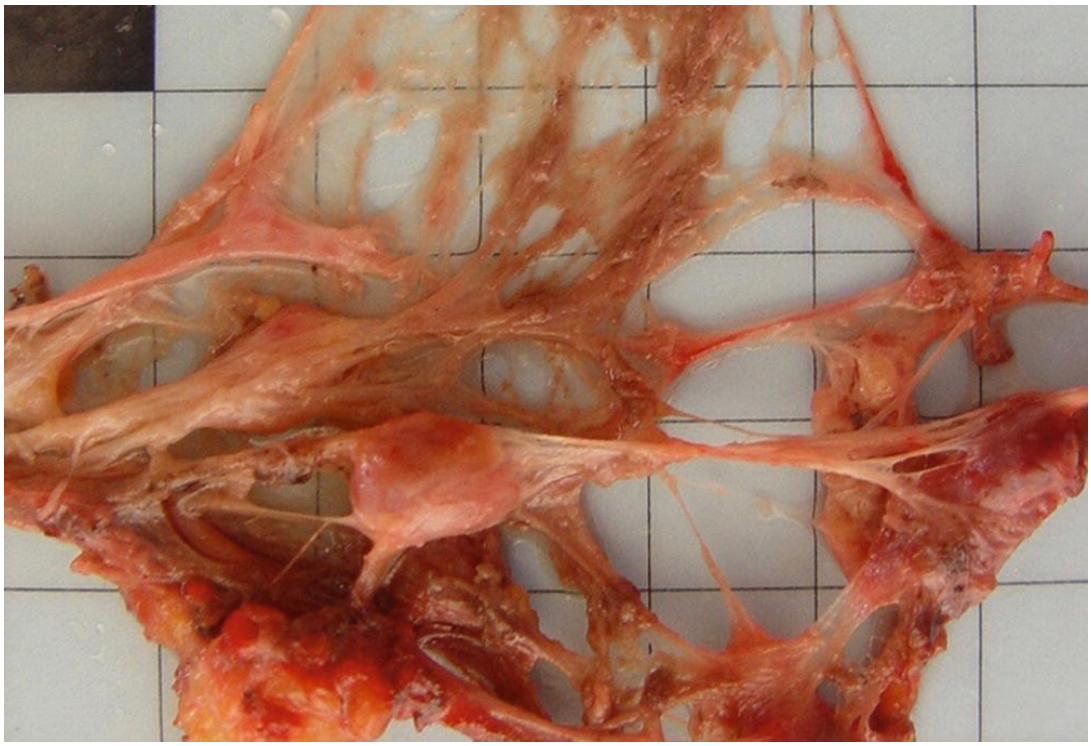

Fig. 3.10 Lymphatic mapping in breast cancer. In the central part of mapping, there is the lymph node up to 12 mm; there is no gross evidence of tumor pathology

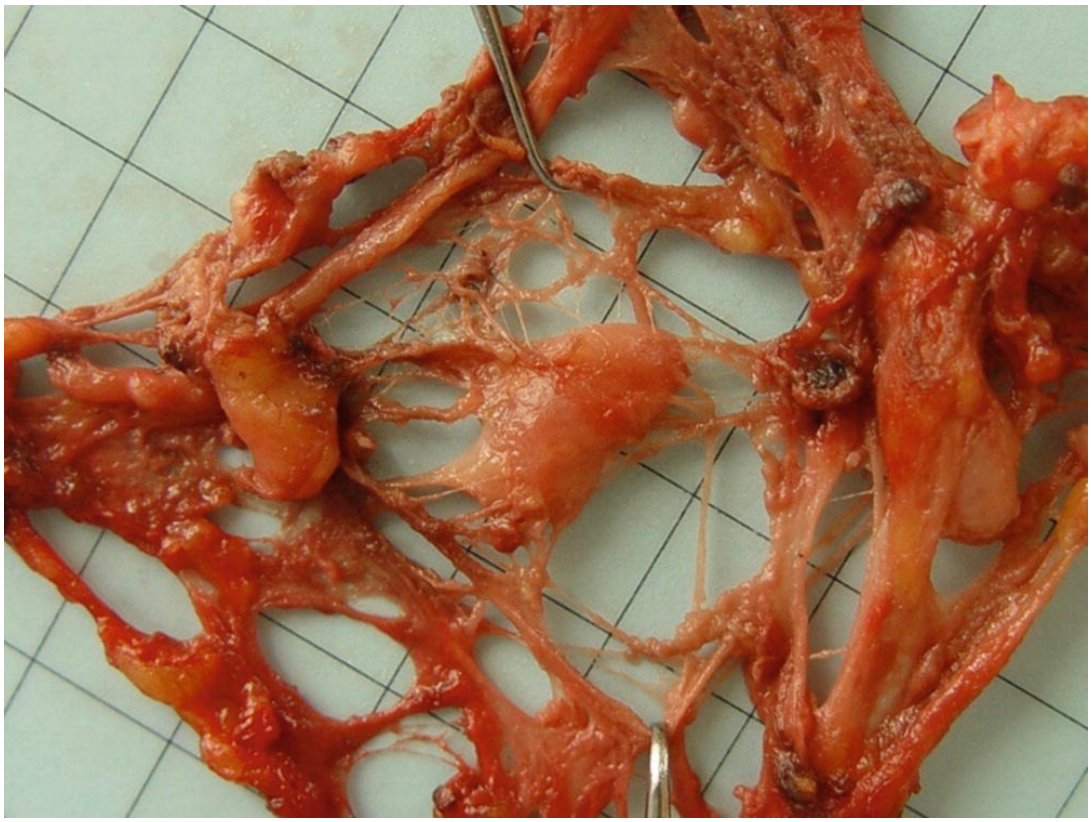

Fig. 3.11 Lymphatic mapping of the axillary region in breast cancer. Surgical hooks open an access to the central node. This lymph node size reaches 15 mm; neo-lymphangiogenesis is active. The node capsule has no signs of metastatic lesion. Efferent vessels are cylindrical and normal in size

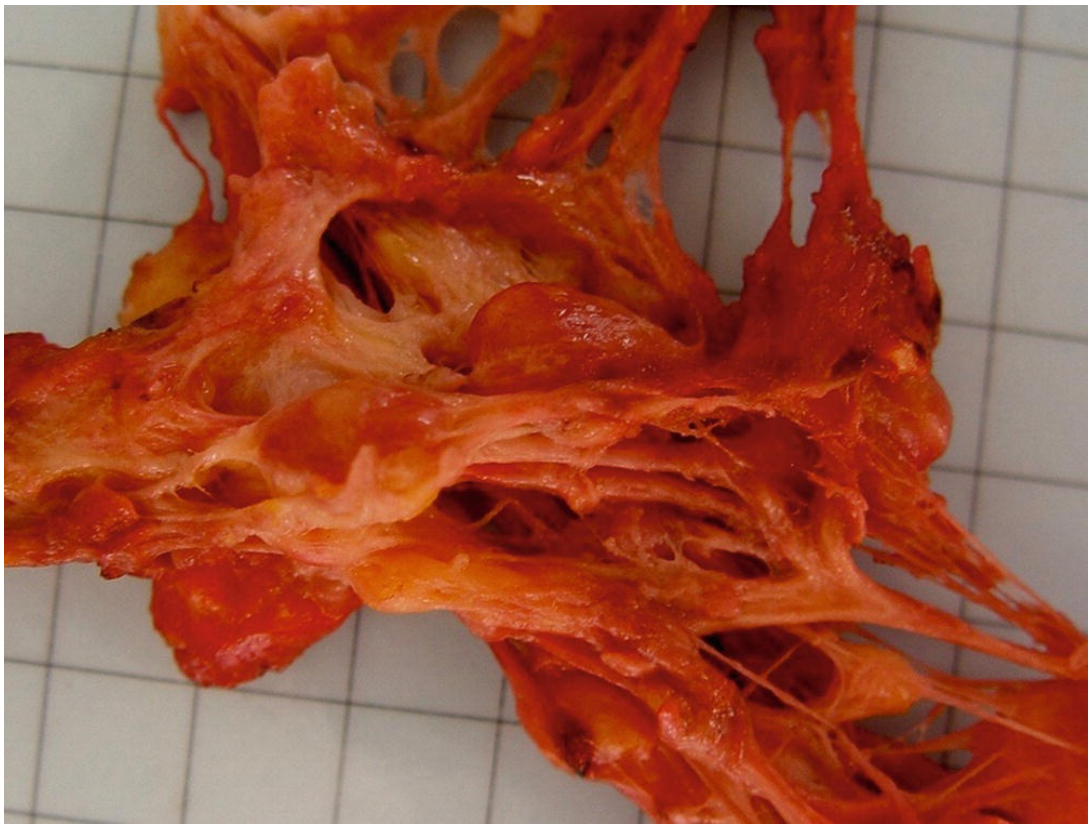

Fig. 3.12 Lymphatic mapping of the axillary region in breast cancer. A stromal component is expressed; it involves all lymph nodes of anatomical region. In this case, lymphatic dissection is difficult

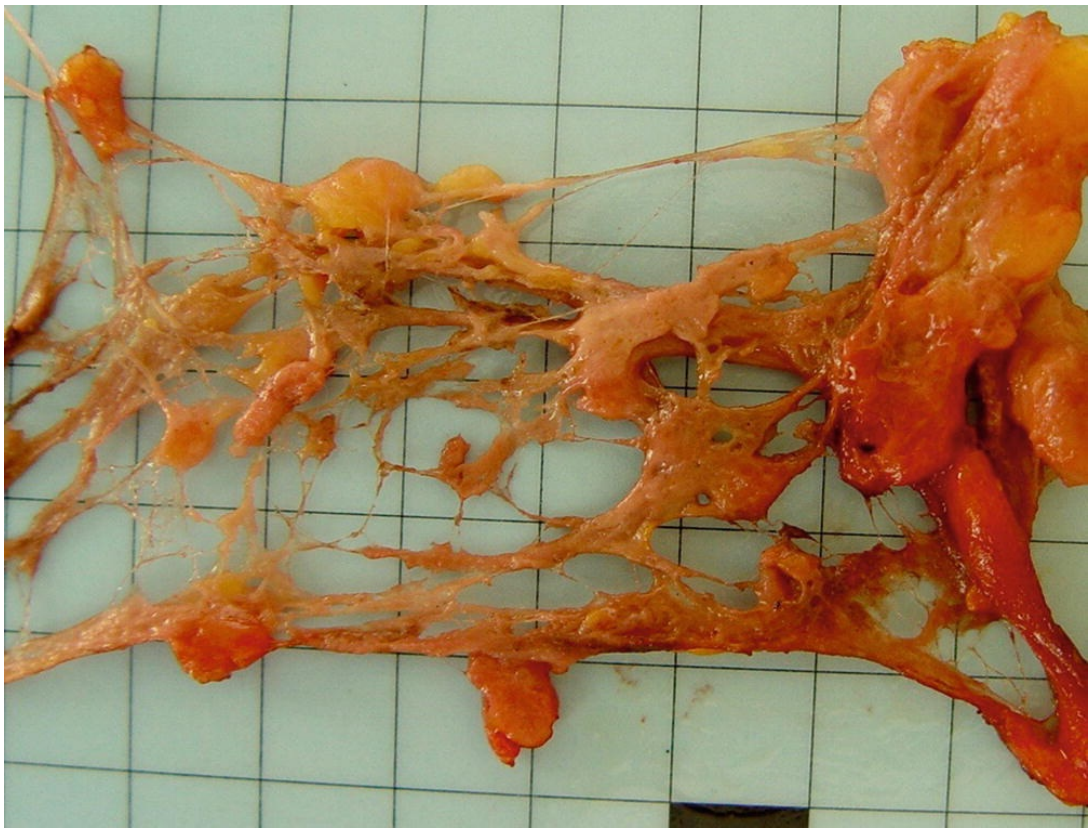

Fig. 3.13 The fragment of lymphatic mapping in breast cancer. There is a network of lymphatic vessels and lymph nodes; their size does not exceed 10 mm. The node capsules contain a large amount of adipose tissue

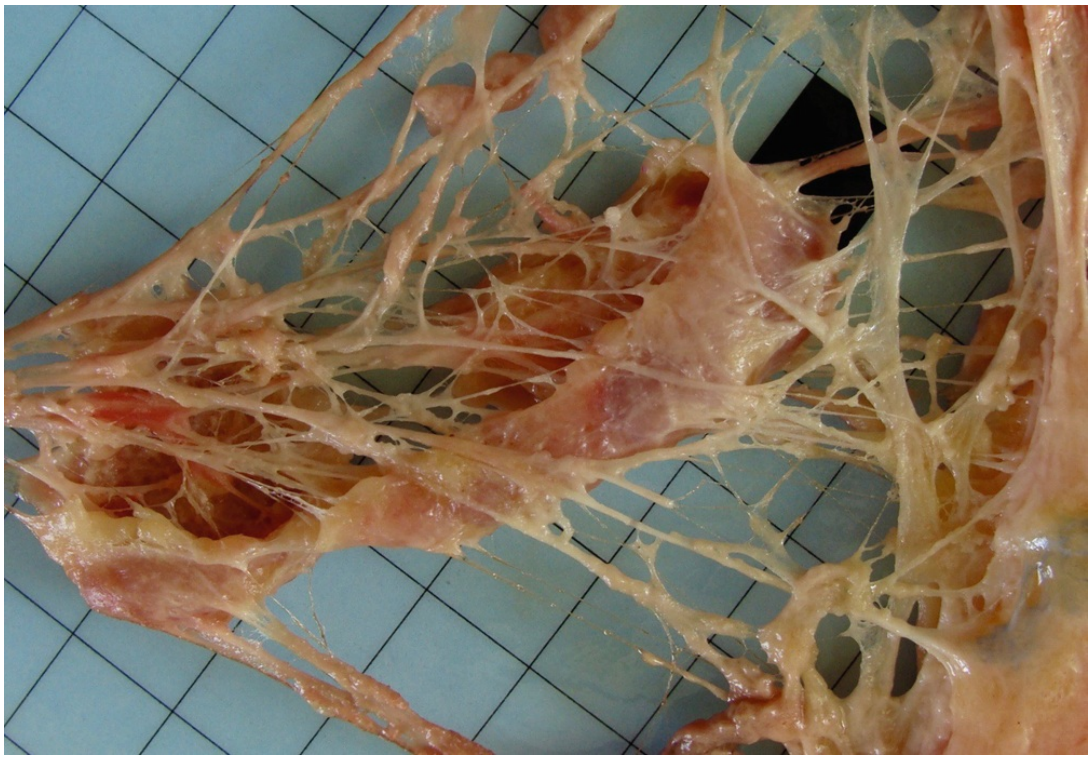

Fig. 3.14 Lymphatic mapping in breast cancer. In the central part of the figure, there is a lymph node up to 40 mm in length. There are a large number of lymphatic vessels of small diameter in the specimen; they are connected with the node, suggesting its functional potential

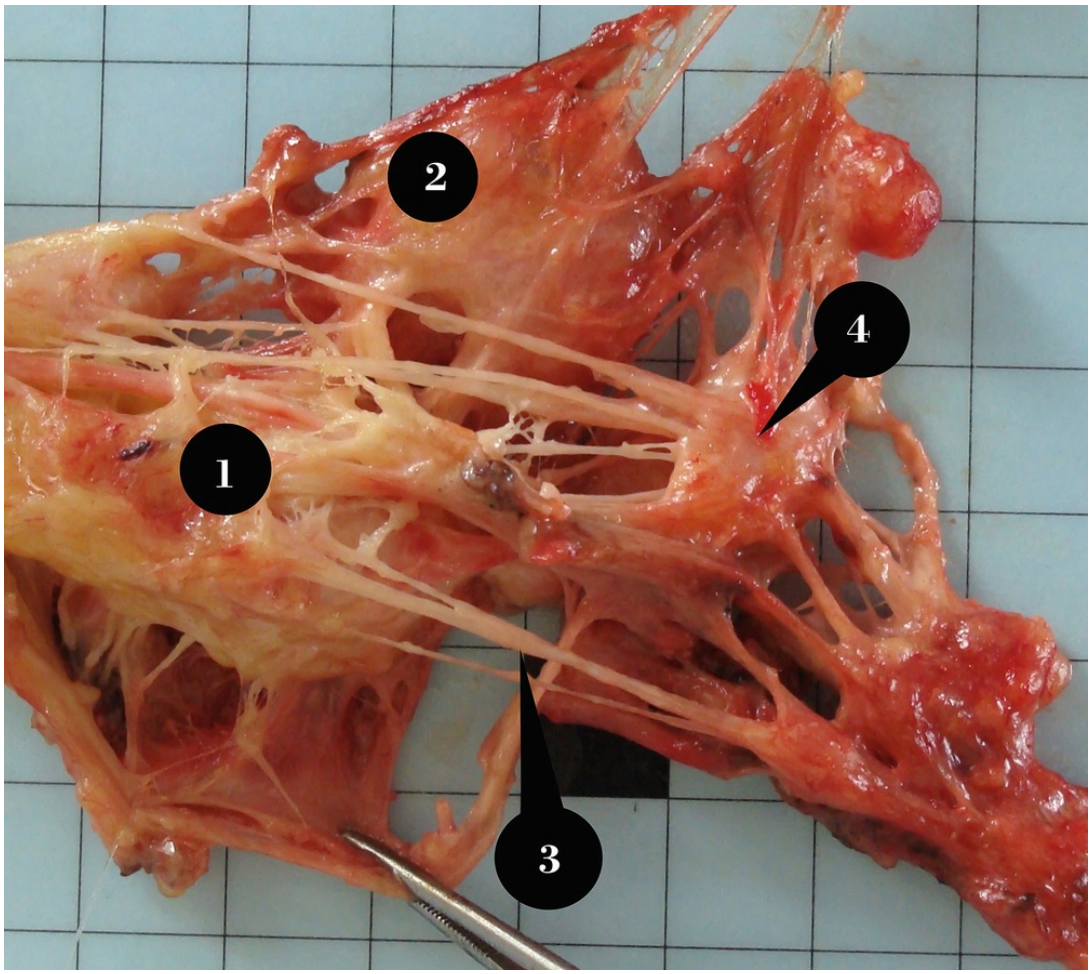

Fig. 3.15 The fragment of lymphatic mapping of the axillary region in breast cancer. Figure 1 illustrates connective tissue cords and vessels (3), including adipose tissue. 2 and 4 illustrate lymph nodes. The 2 node is enlarged; the capsule is slightly changed. The 4 node has more significant changes; the vessels that are flown to it are enlarged and tense

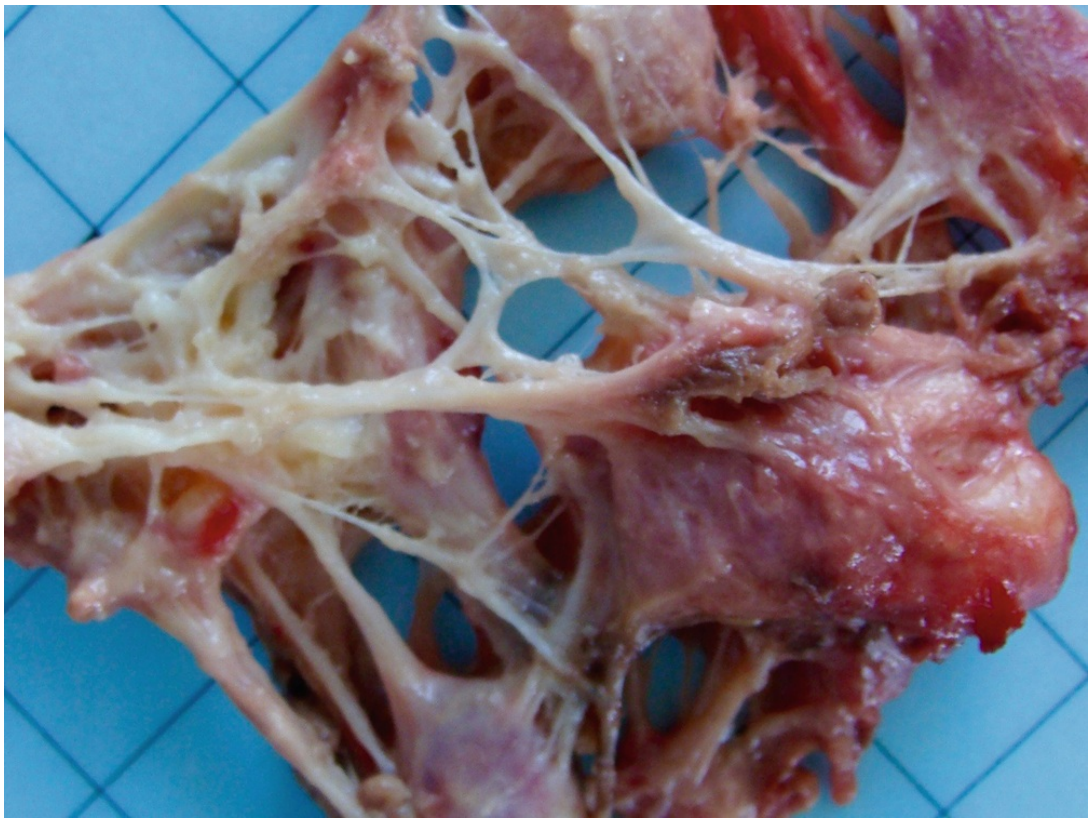

Fig. 3.16 Lymphatic mapping. There is a sentinel lymph node surrounded by well-formed vessels in proximal segment. There are practically no newly formed vessels. The node capsule has significant pathological changes, characteristic for metastatic disease

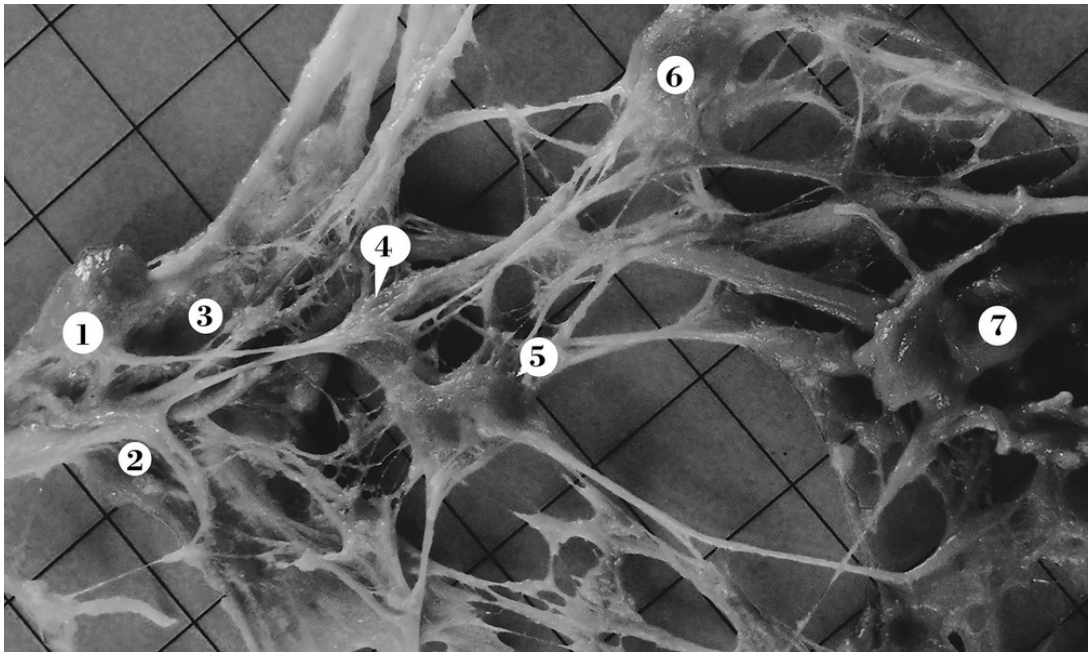

Fig. 3.17 Black and white film allows studying some details of anatomical complexes better than in color format. Figures 1, 4, 5, 6, and 7 illustrate lymph nodes in different state and status and 2,3 – soft tissue components and vessels. The 5 lymph node is surrounded by numerous newly formed vessels which indicate its functional activity. In its center, there is an umbilication – a sign of metastatic lesion with a transition to the capsule

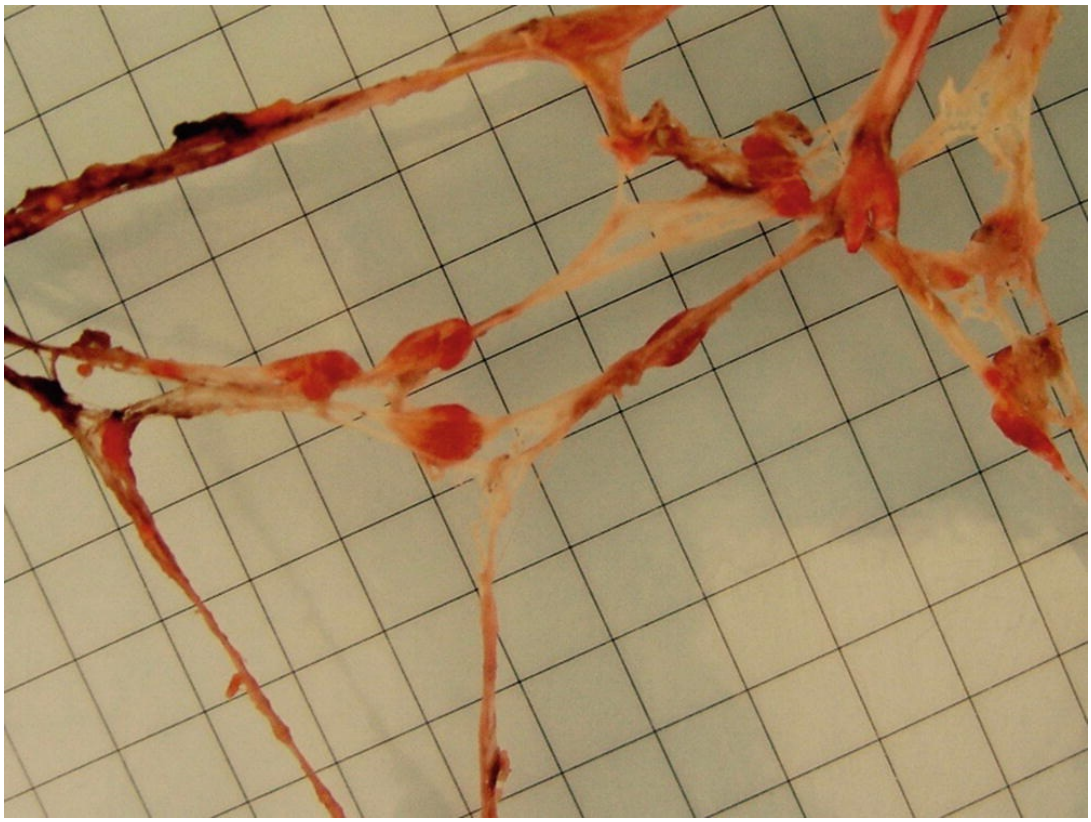

Fig. 3.18 The fragment of lymphatic mapping in breast cancer. There are several lymph nodes and the great lymphatic and blood lines

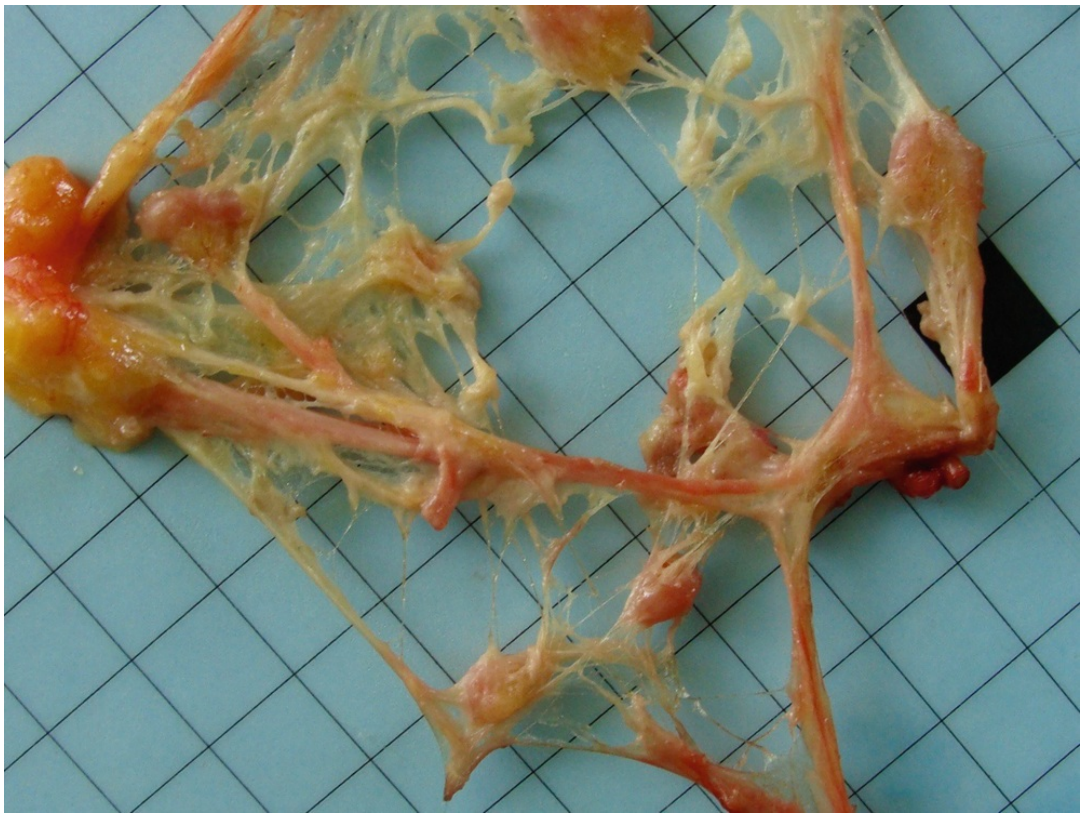

Fig. 3.19 Lymphatic mapping of the axillary region after ultrasonic dissection. The stroma is moderately expressed. Neo-lymphangiogenesis is not active. Lymph nodes are not numerous and mostly no more than 5 mm

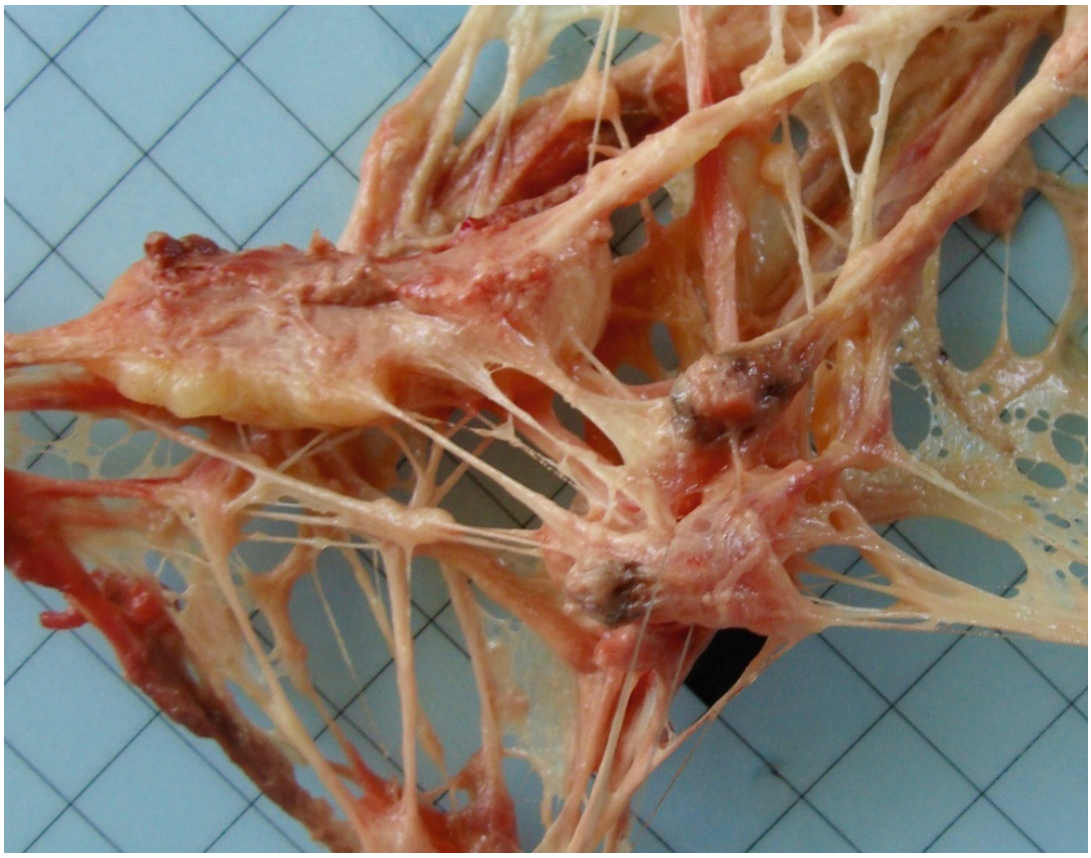

Fig. 3.20 The proximal segment of lymphatic mapping, which is filled with a large number of deformed and scarry transformed nodes with many lymphatic vessels. The sentinel lymph node is elongated and reaches 40 mm; the other nodes are smaller

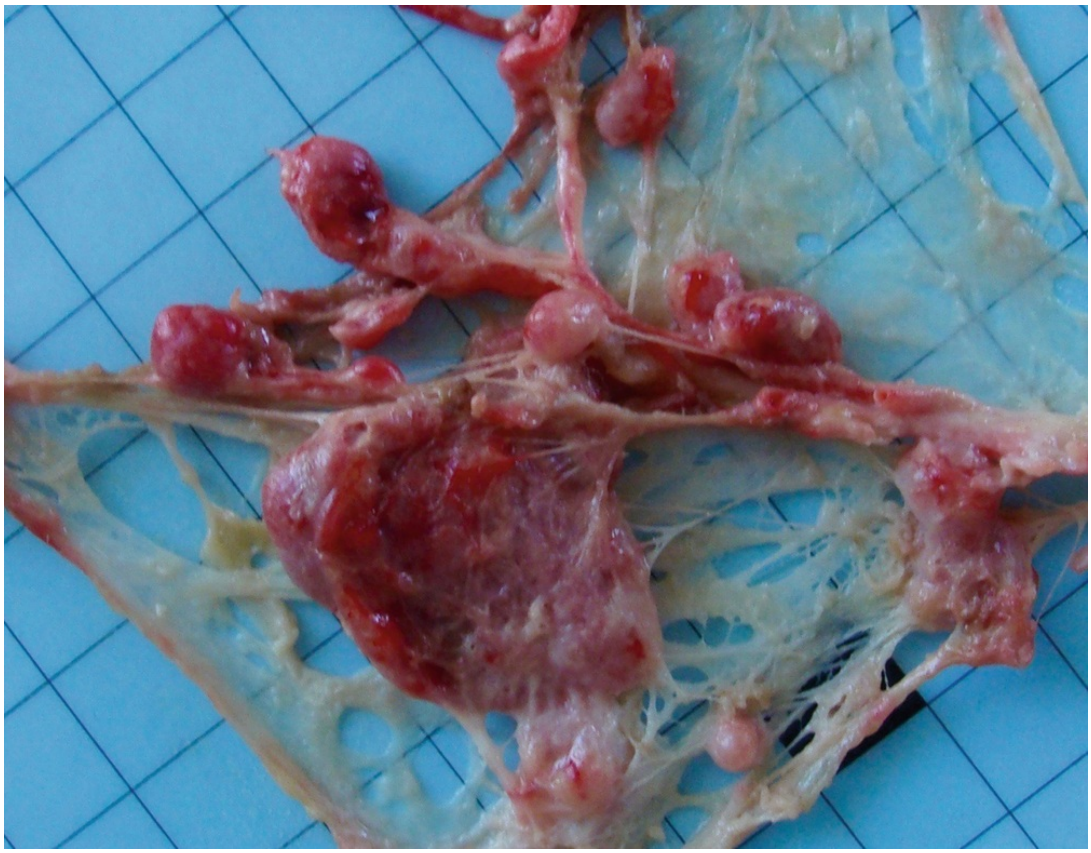

Fig. 3.21 Lymphatic mapping with many lymph nodes. In the central zone of the specimen, there is a sentinel lymph node after planar resection of its portion. This allows seeing the node parenchyma and many inflow lymph vessels that penetrate into sinuses. There are nodal formations in parenchyma. Neo-lymphangiogenesis is active

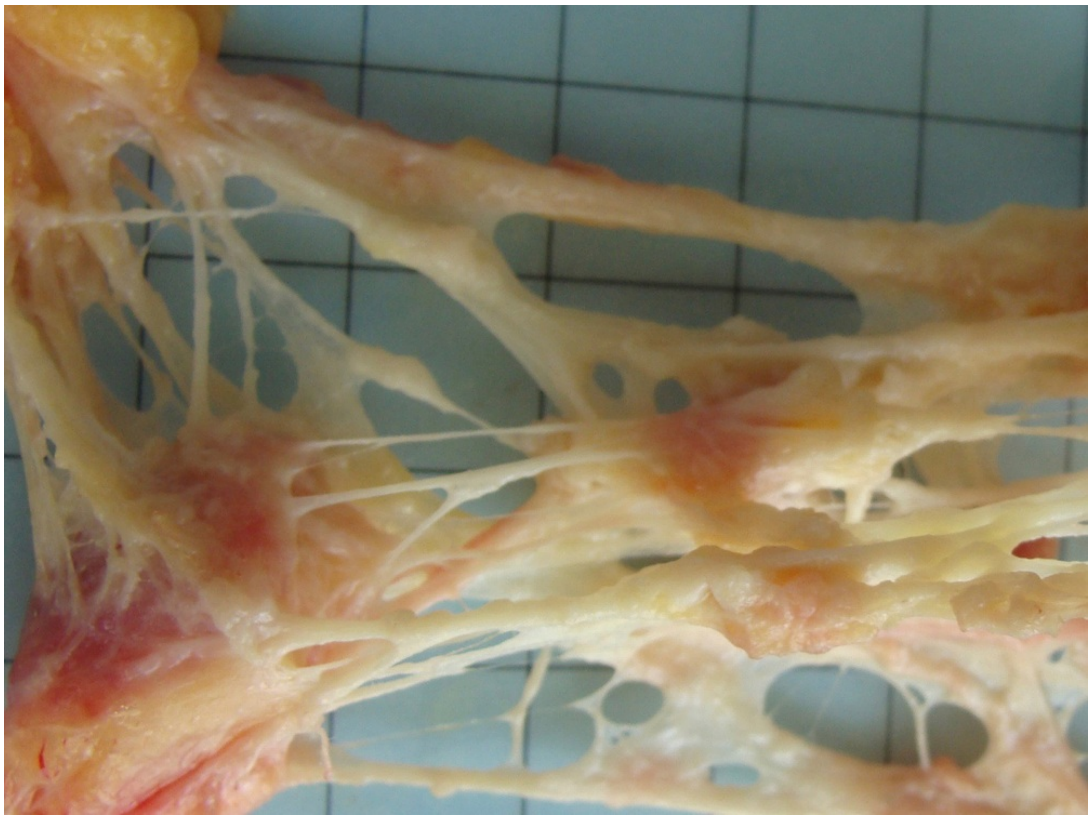

Fig. 3.22 The fragment of lymphatic mapping. The stroma is expressed; tubular structures are well-formed: blood and lymphatic vessels. Lymph node is up to 10 mm with well-formed lymph affluxion system. The capsule is inhomogeneous, with pale areas

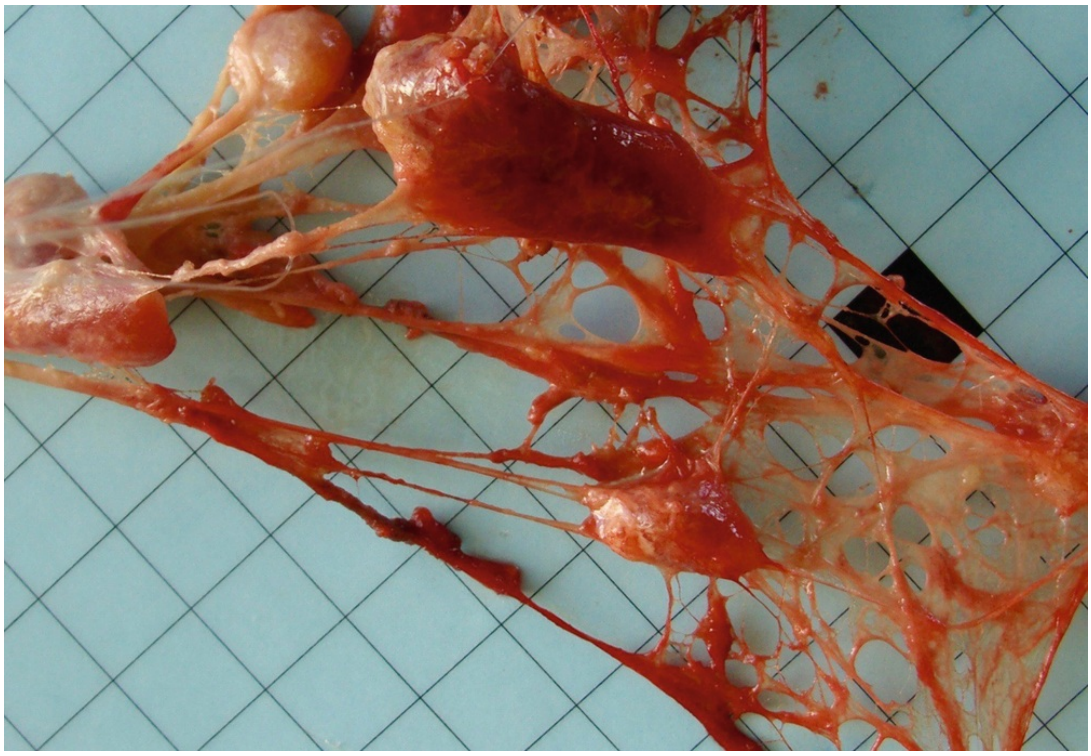

Fig. 3.23 Lymphatic mapping in breast cancer. A few large nodes are visible. The stromal component is not significantly expressed and includes a tender connective tissue. In the proximal zone, the vascular pattern is not significantly expressed, but in the distal zone, it is evidenced a lymphatic plexus forming network

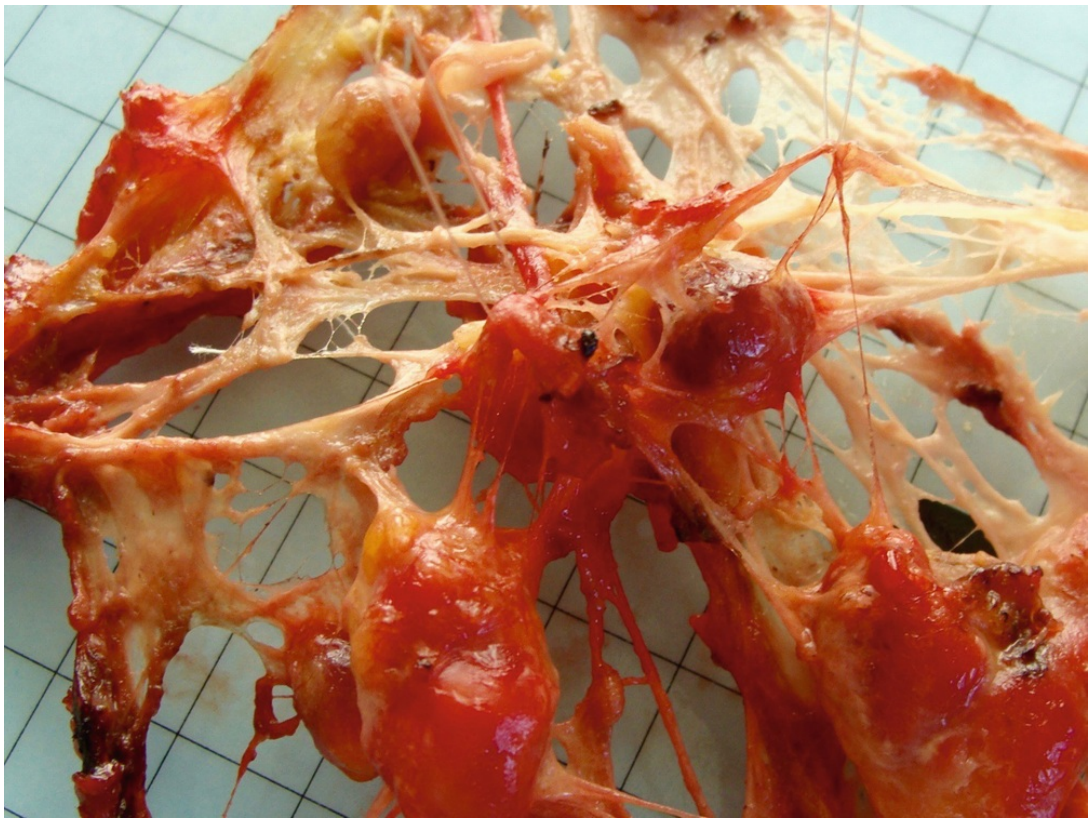

Fig. 3.24 The central zone of lymphatic mapping, where the lymph nodes are grouped. Nodes have different sizes; some form conglomerations. Vasculature is well-developed, mainly due to native formations

Fig. 3.25 The proximal segment of lymphatic mapping, including the sentinel lymph node. This node is matted to another one, forming conglomeration. The great tubular structures are well-formed

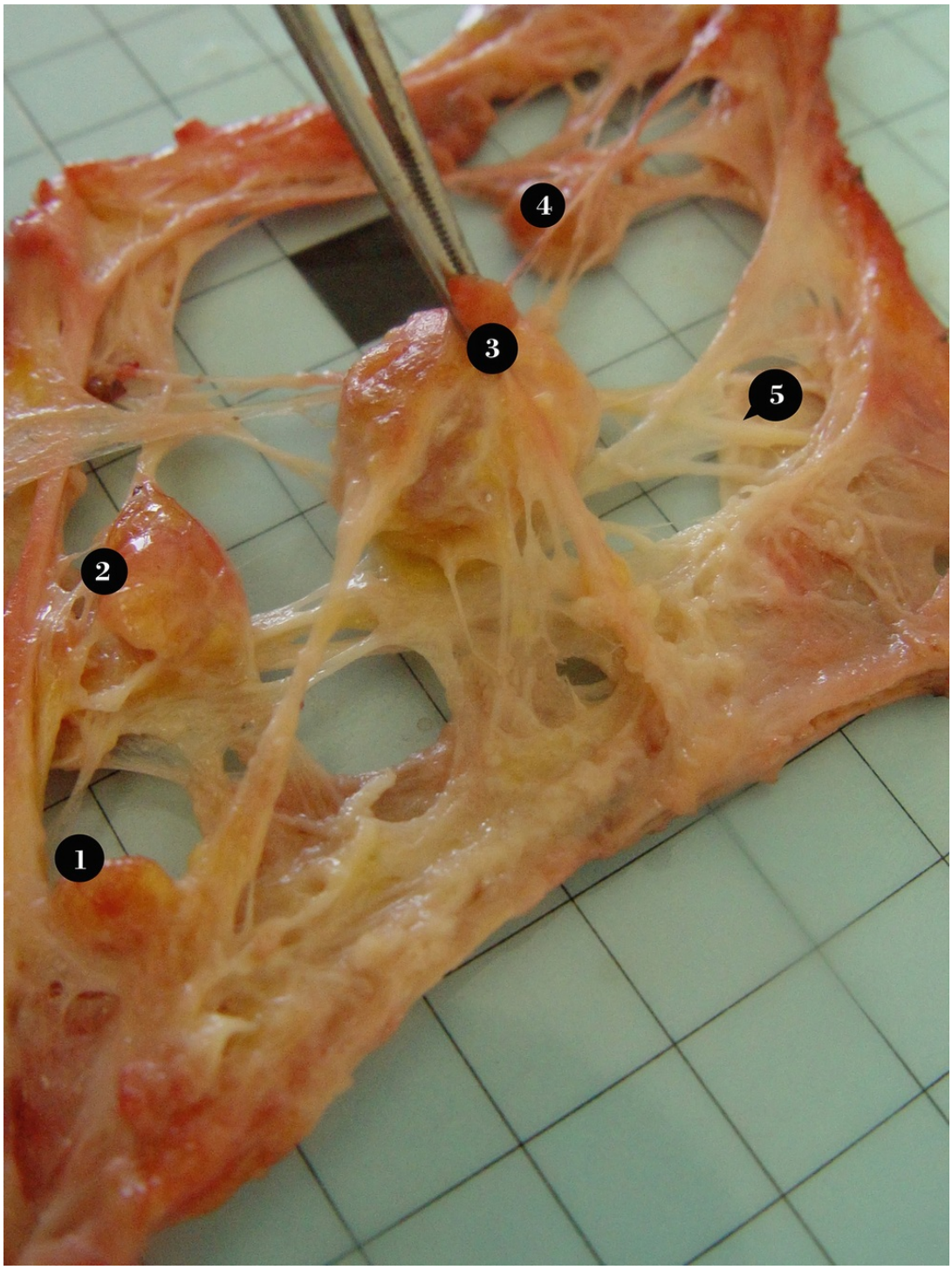

Fig. 3.26 The central zone of lymphatic mapping with lymph nodes (1,2,3,4). The 3 lymph node is susceptible to the most significant changes; neo-lymphangiogenesis is active. Lymphatic vessel density is moderate (5)

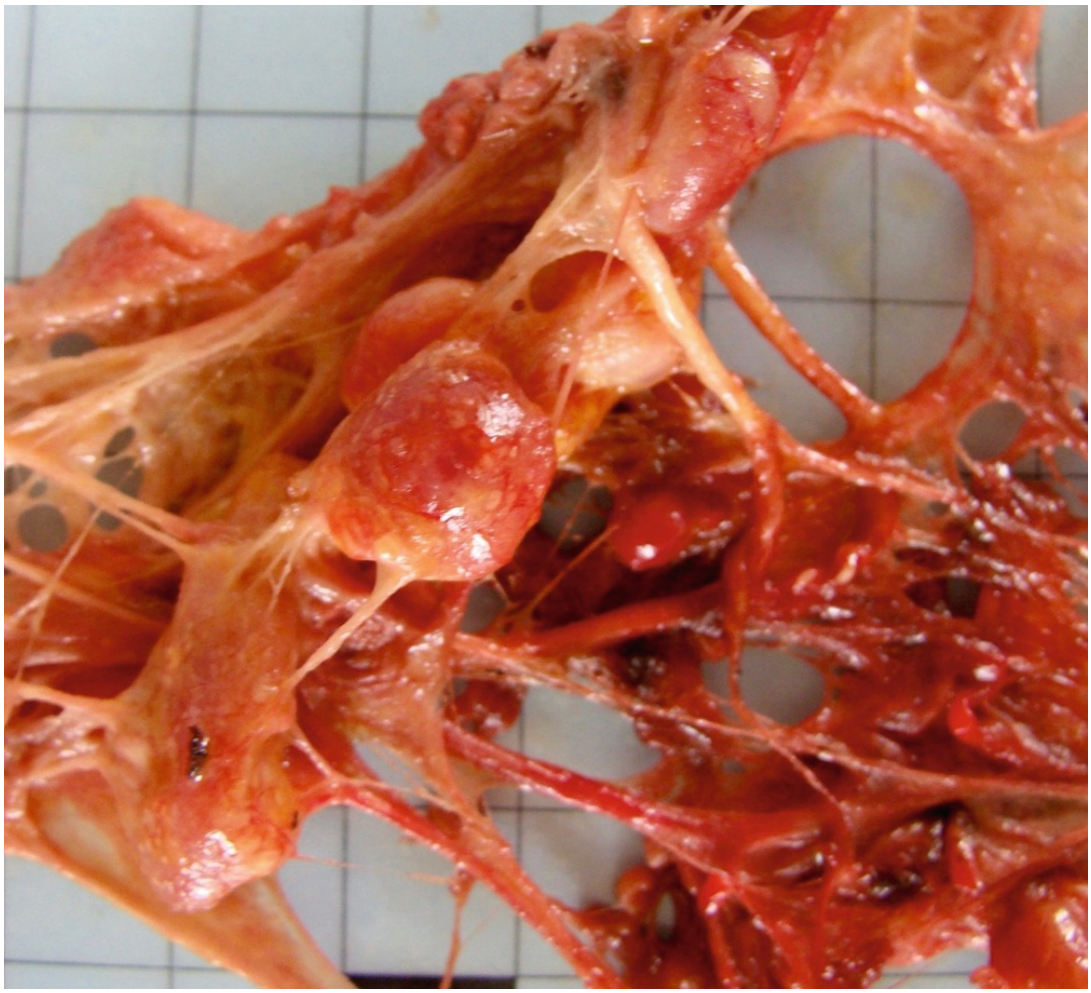

Fig. 3.27 Cascade of lymph nodes in the central zone of lymphatic mapping. The size and shape of the lymph nodes vary in a distal direction. The great vessels are cylindrical and well-formed, suggesting a preserved zonal lymphatic perfusion

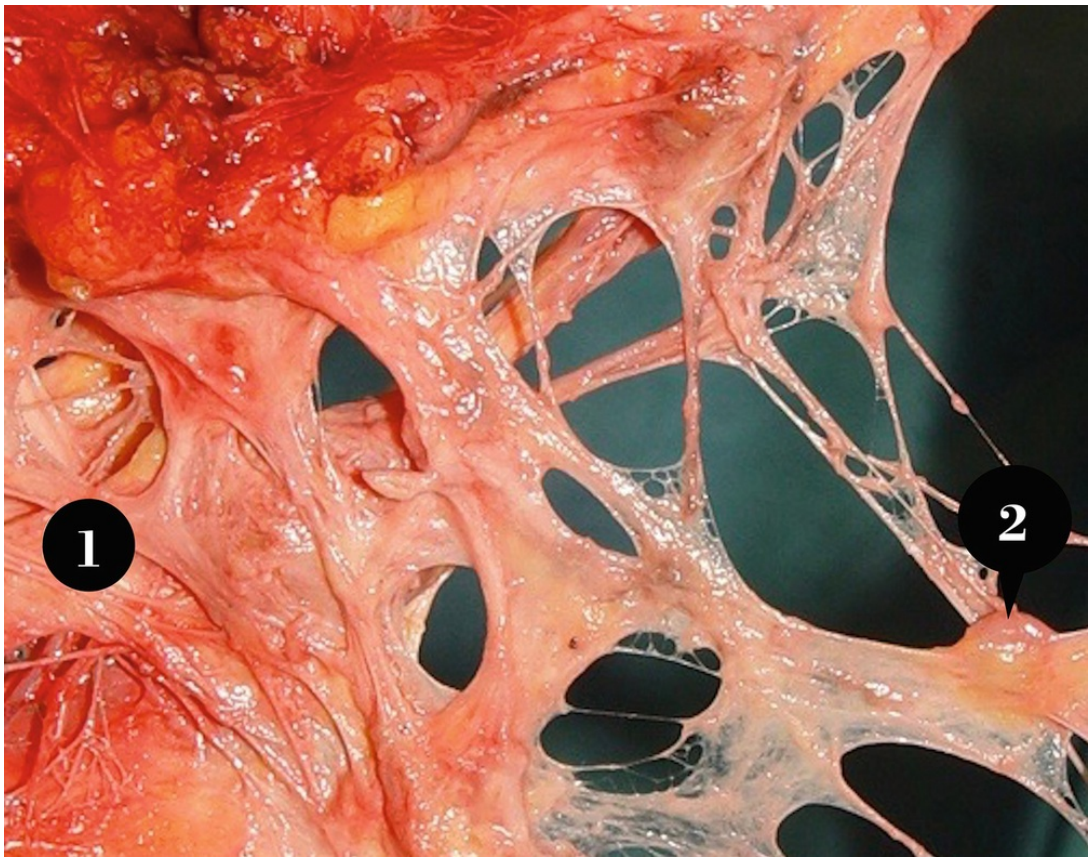

Fig. 3.28 The fragment of the lymphatic mapping of the axillary region. There is a massive connective tissue transformation (1) after removal of adipose tissue. The vascular pattern is not clearly expressed. There is a round-shaped lymph node (2) in membranous structures; its capsule has a normal color

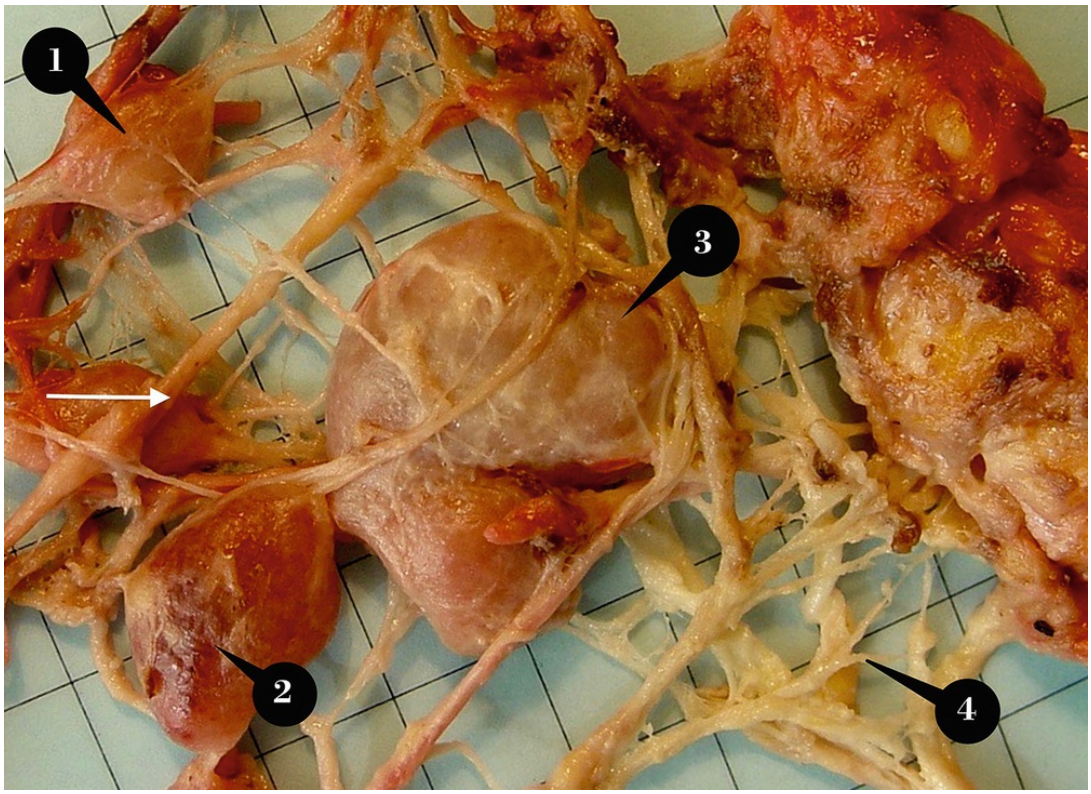

Fig. 3.29 The anatomical complex, a fragment of lymphatic mapping of the axillary region in stage III breast cancer. The arrow indicates the direction of the main lymph efflux from the mammary gland. Figures 1, 2, and 3 illustrate the lymph nodes of different size and the grade of lesion by neoplastic process. In the projection, there are several nodes (a total size of about 50 mm) with significant changes located from 1 to 4 o'clock position on the dial. The vessels that surround this group also have significant abnormalities, their diameter is increased, and there are portions of narrowing

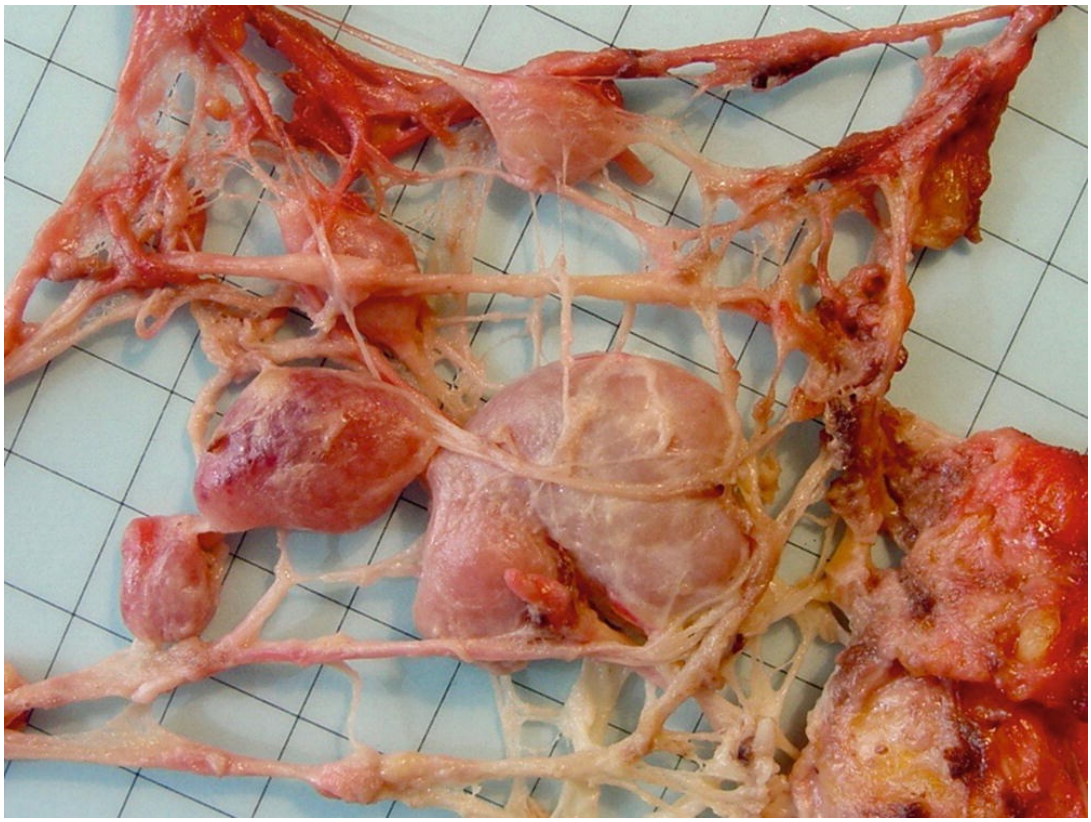

Fig. 3.30 Lymphatic mapping of the axillary region in breast cancer. There are enlarged lymph nodes of all main basins. The nodes' size reaches 25–30 mm. Some of the nodes have signs of secondary metastatic cancer. The stroma is not expressed

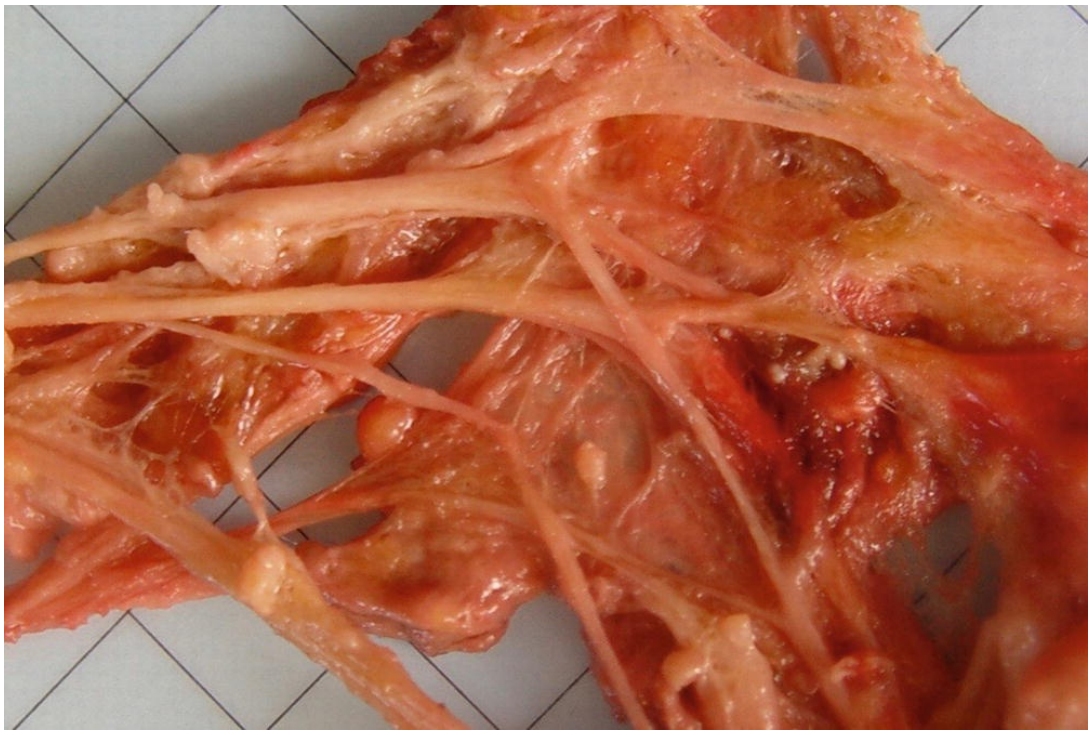

Fig. 3.31 Lymphatic mapping of the axillary region after lymphatic dissection. There are the main lymphatic basins and lymph nodes reaching 5 mm. The stromal component is significantly expressed

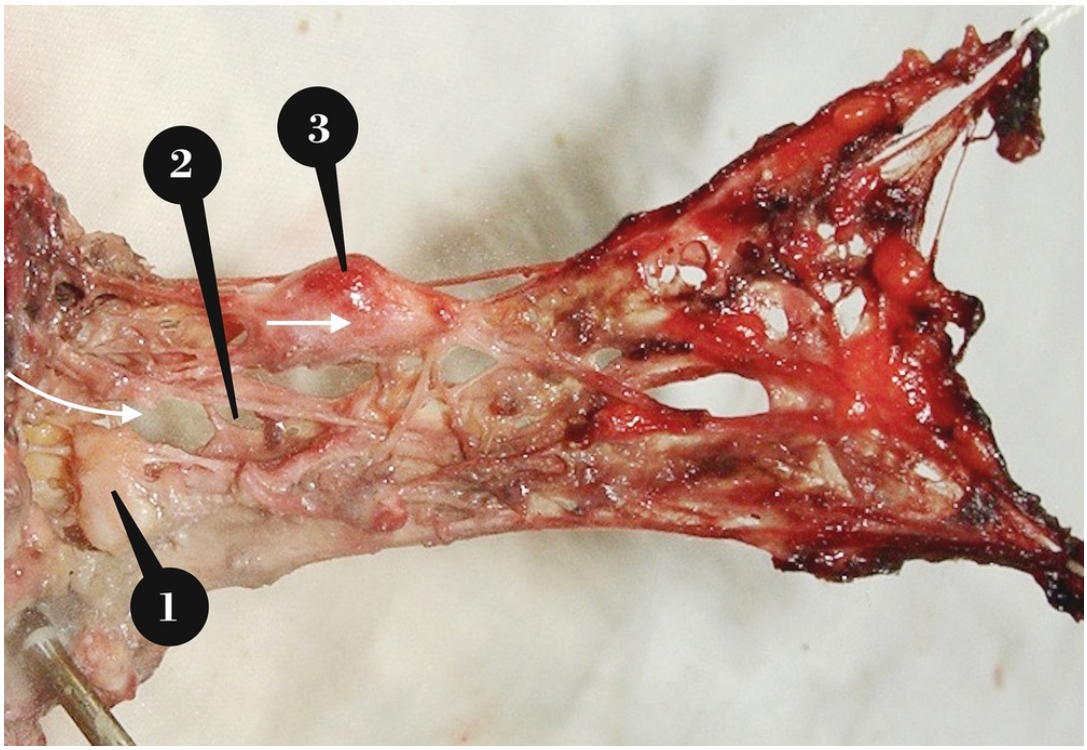

Fig. 3.32 The final stage of axillary fat lymphatic dissection. In order to have a clear idea of the logistics of metastasis, it is necessary to project the specimen correctly from anatomical region. The figure illustrates the final stage of adipose tissue specimen and formation of an individual anatomical mapping (patient-specific anatomy). 1 enlarged lymph node with vessels not exceeding the normal number. 2 medium-axillary vascular trunk; lymph nodes are not visible in its basin. 3 enlarged and tense lymph node with a modified capsule due to its metastatic lesion. In surgical area, there is also a catheter for dissection

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4. Lymphatic Drainage: Lymphangiogenesis in Cancer

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Keywords Lymphatic system – Axillary lymphatic apparatus – Breast cancer – Lymphatic drainage – Lymphatic vessel – Lymphography – Lymphangiogenesis

The human consists of a huge number of cells, lymphatic and blood vessels, capillaries, and much more. The number of tubular structures in a definite proportion and with intraluminal pressure allows providing homeostasis, so all systems and organs function in the prescribed and necessary mode. The lymphatic system plays a great role both in utilization of decay products and as a regulatory mechanism. In cancer, this role is affected. This is associated with an increase in the load of drainage-depositing units of the lymph microcirculation, increase of metabolic

processes, tumor decomposition, and much more. A brief overview of the lymphatic apparatus status in cancer can be described as the system functioning in extreme conditions. This means that the biological system reacting to a specific situation makes its own adjustments, trying to level out the imbalance of lymphatic drainage by increasing the number of new lymphatic vessels. Currently, this phenomenon is well studied, but there are some differences of opinions concerning prognostic factors and long-term effect of neo-lymphangiogenesis. Research in this direction is on the rise and appeals both clinicians and researchers.

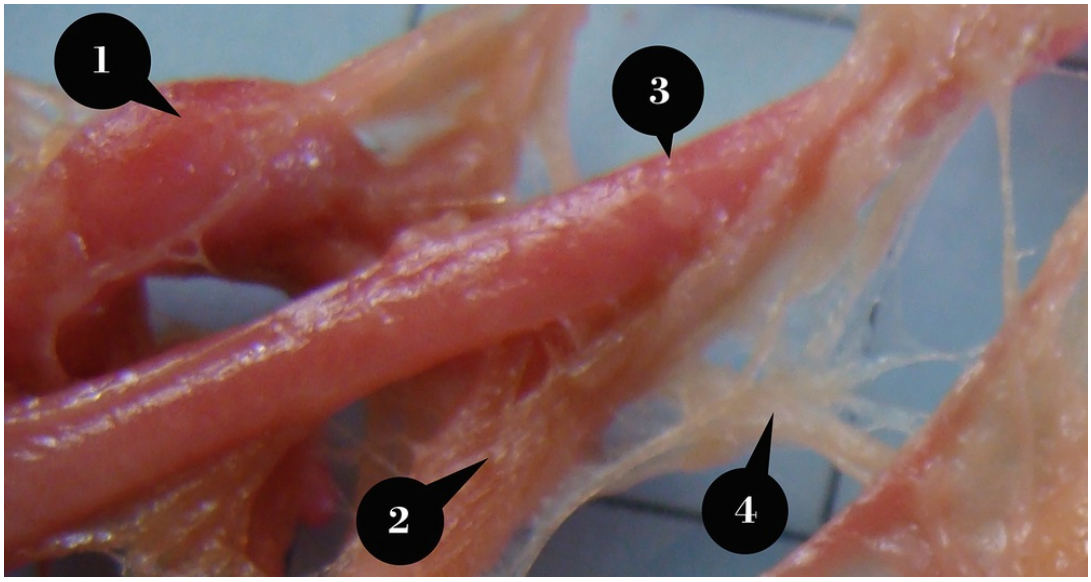

Fig. 4.1 The fragment of lymphatic apparatus of the axillary region: 1 lymph node, 2 lymphatic trunk, newly formed lymphatic vessels (4), and 3 arterial trunk

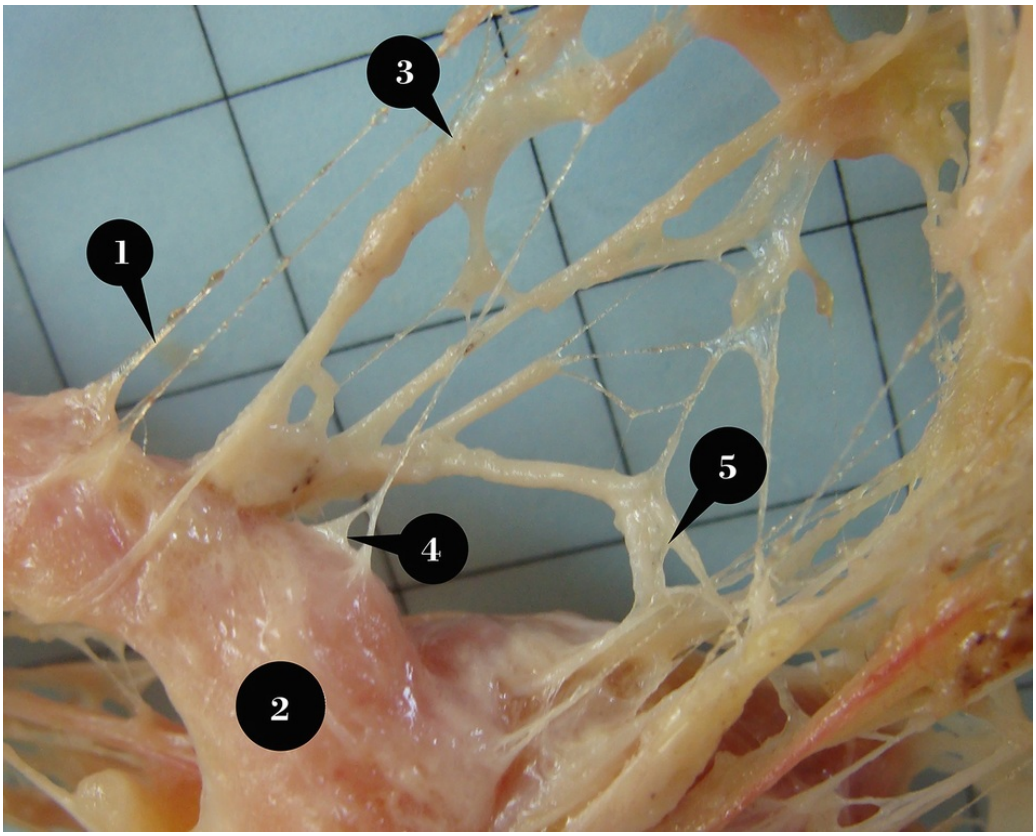

Fig. 4.2 The specimen demonstrates a fragment of the lymph node (2). The node capsule is unevenly colored, with scar inclusions. There are visible lymphatic vessels (1,3,4,5) of different diameters and structures

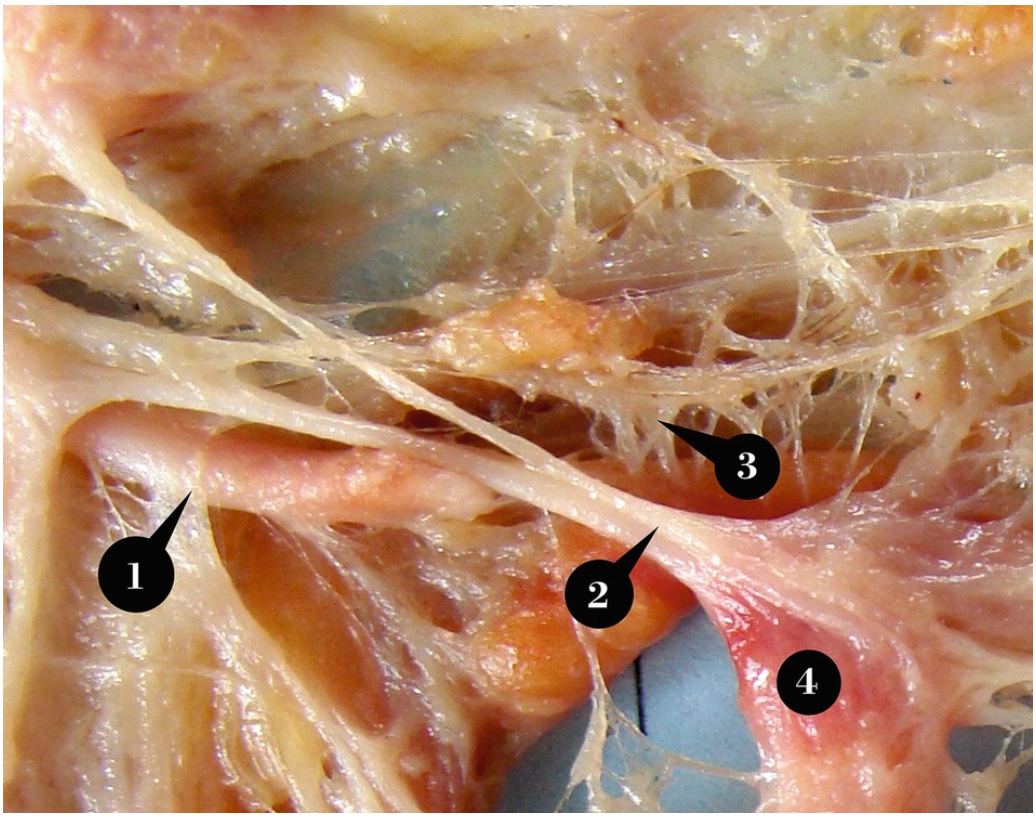

Fig. 4.3 The fragment of lymphatic mapping of the axillary region. A stromal component is expressed. Figure 1 illustrates a blood vessel, 2 inflow lymphatic vessels, 3 multiple newly formed collateral lymphatic vessels, and 4 the lymph node with a capsule which is inhomogeneous, sometimes with fat deposits

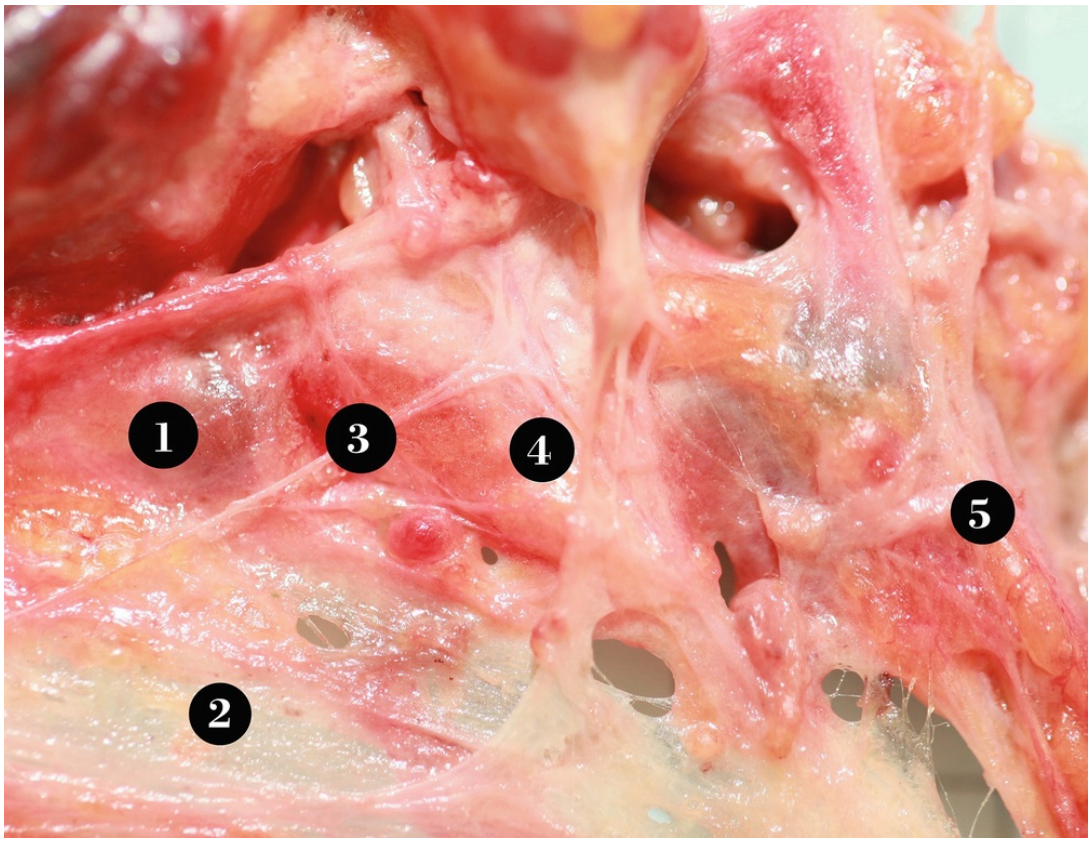

Fig. 4.4 The fragment of anatomical complex of the axillary region after surgical dissection. The stromal component (2) is expressed. Lymph nodes form a single conglomeration (1, 4, etc.), the size reaches 25 mm, and there are several visible nodes of 2–3 mm. Figure 3 illustrates a newly formed transient vessel and 5 the great vessels

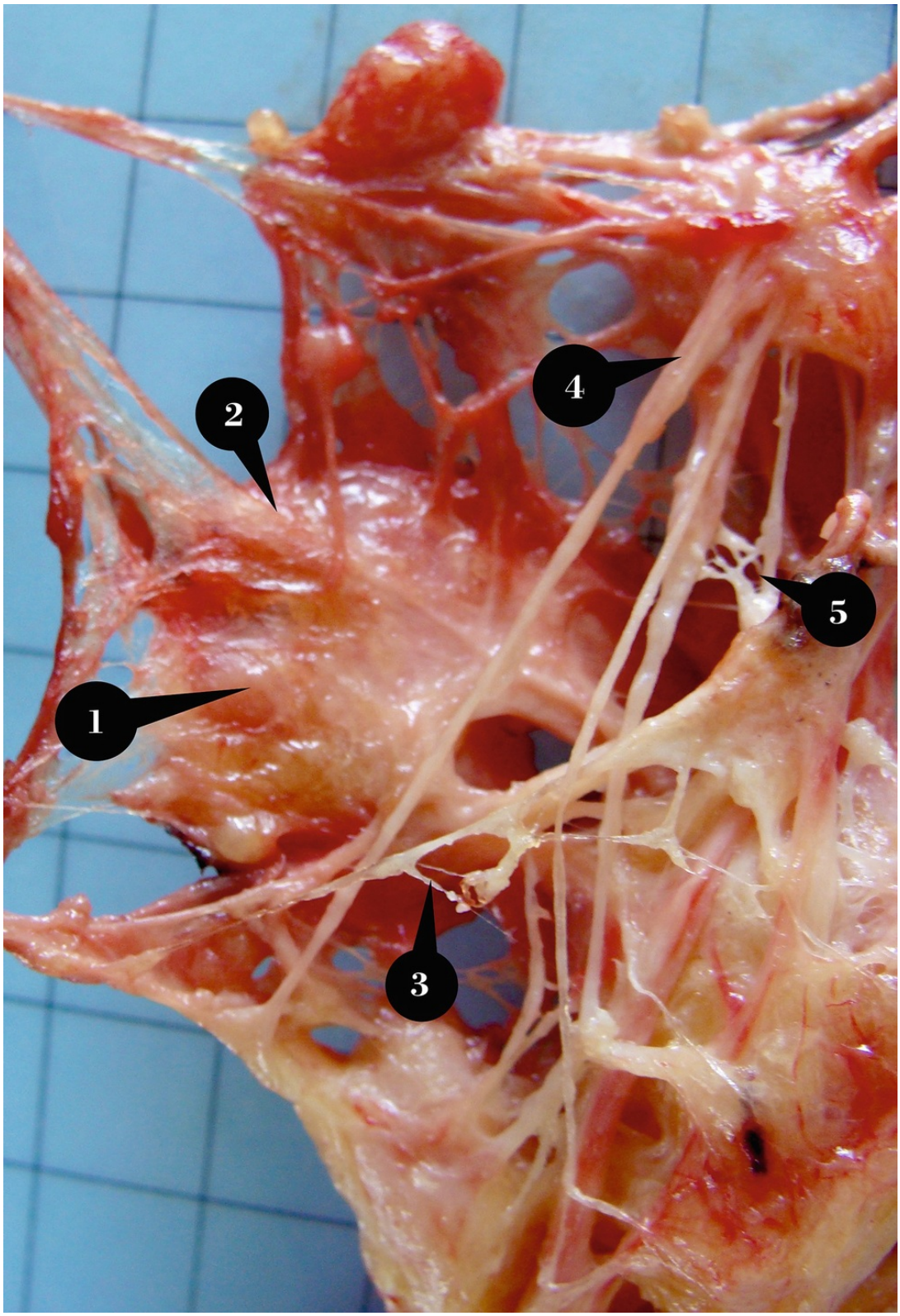

Fig. 4.5 In an anatomical specimen, there are a large number of lymphatic vessels (high vessel density) of various diameters and a functional site of

action (2,3,4,5). The 1 lymph node is with signs of metastatic disease; the capsule is inhomogeneous and tuberous

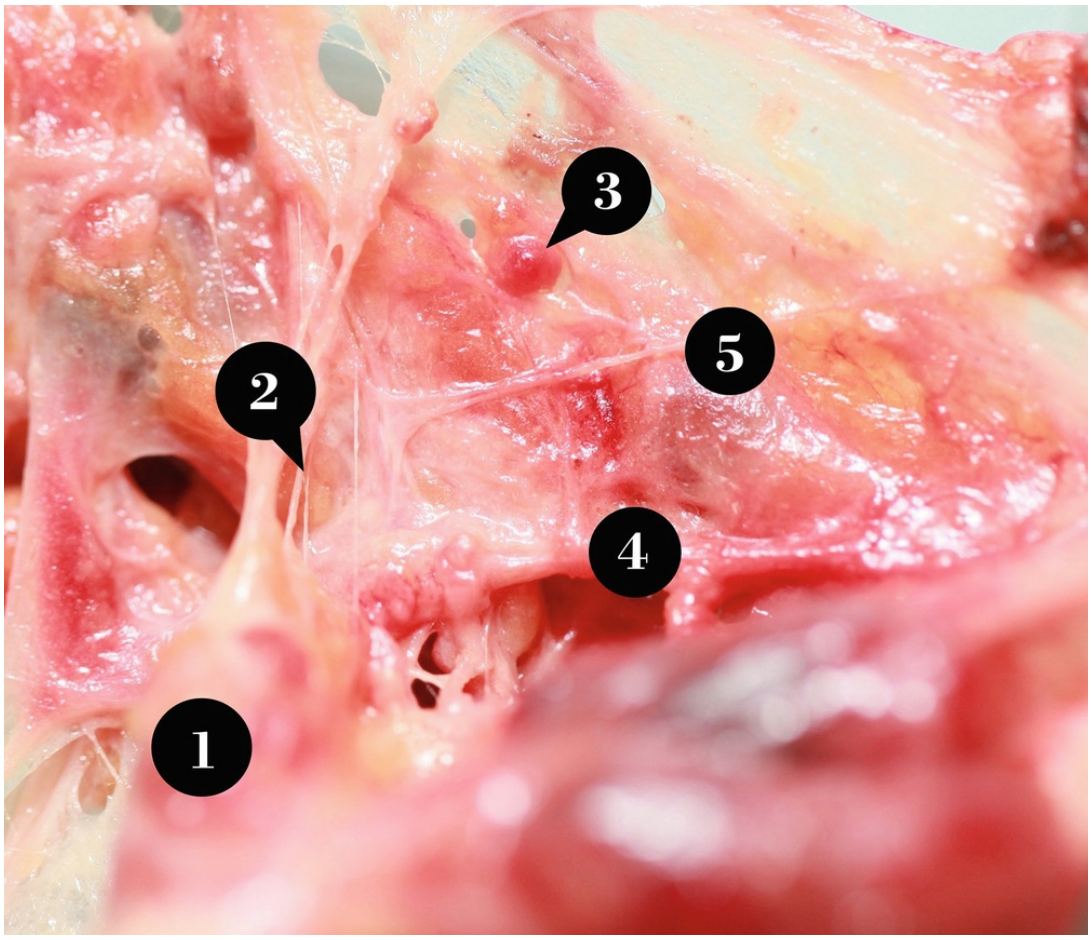

Fig. 4.6 Anatomical complex of the axillary region in breast cancer. There is a significant stromal component that does not respond to ultrasonic destruction. Figures 1, 4, and 5 illustrate the lymph nodes and 2 illustrates arterial trunks and 3 newly formed lymphatic vessel

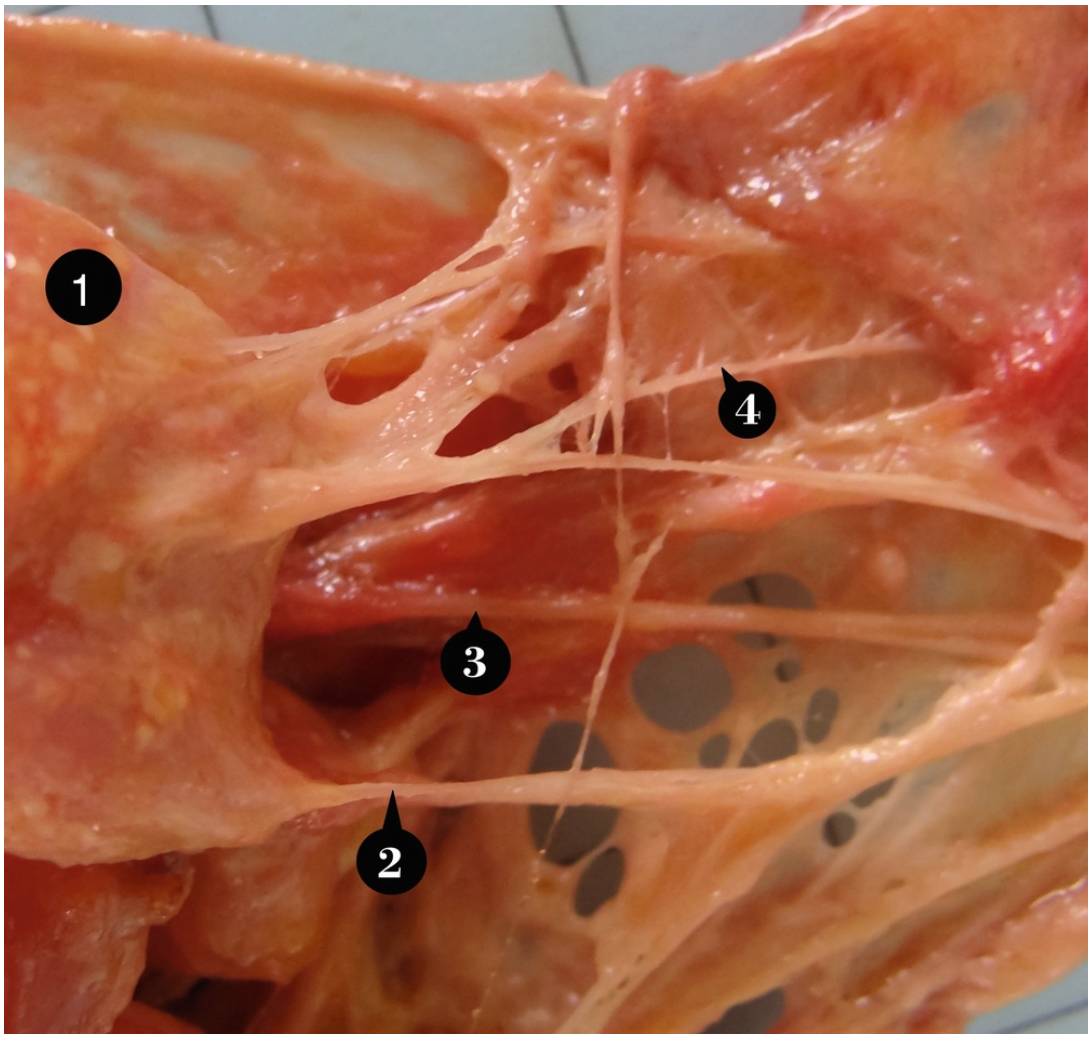

Fig. 4.7 At the picture there are the lymph node (1), different lymphatic vessels (2, 4), and blood vessels in the hilar area (3). The lymph node capsule is with pale portions and indurations. The stromal component is expressed. This symptom is characteristic for patients who had preoperative radiation therapy

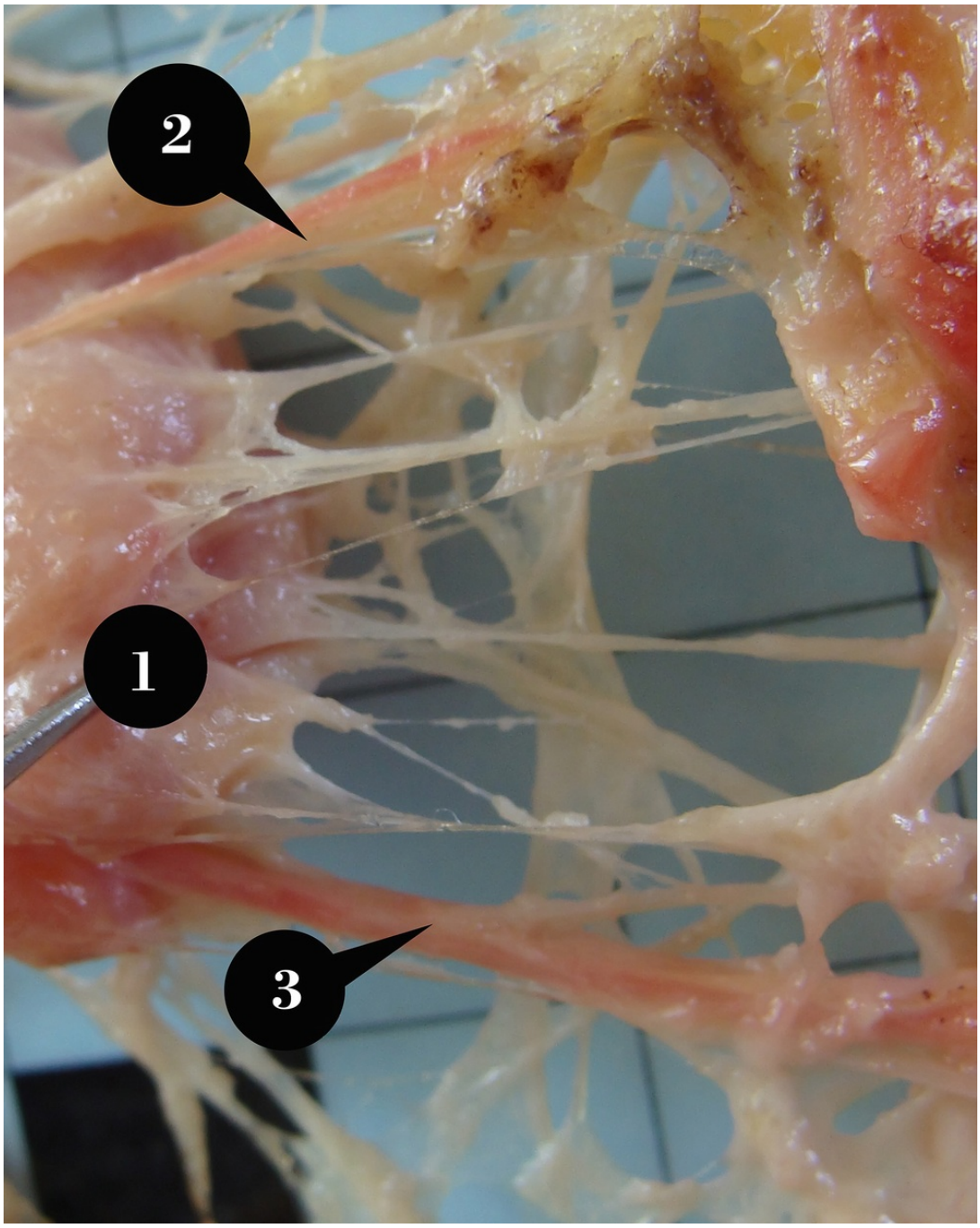

Fig. 4.8 Multiple lymphatic vessels (1,2) connected with the lymph node and 3 – transient lymphatic vessel. Vessels differ in their size and intensity. Most of the vessels have no the same diameters and uneven walls

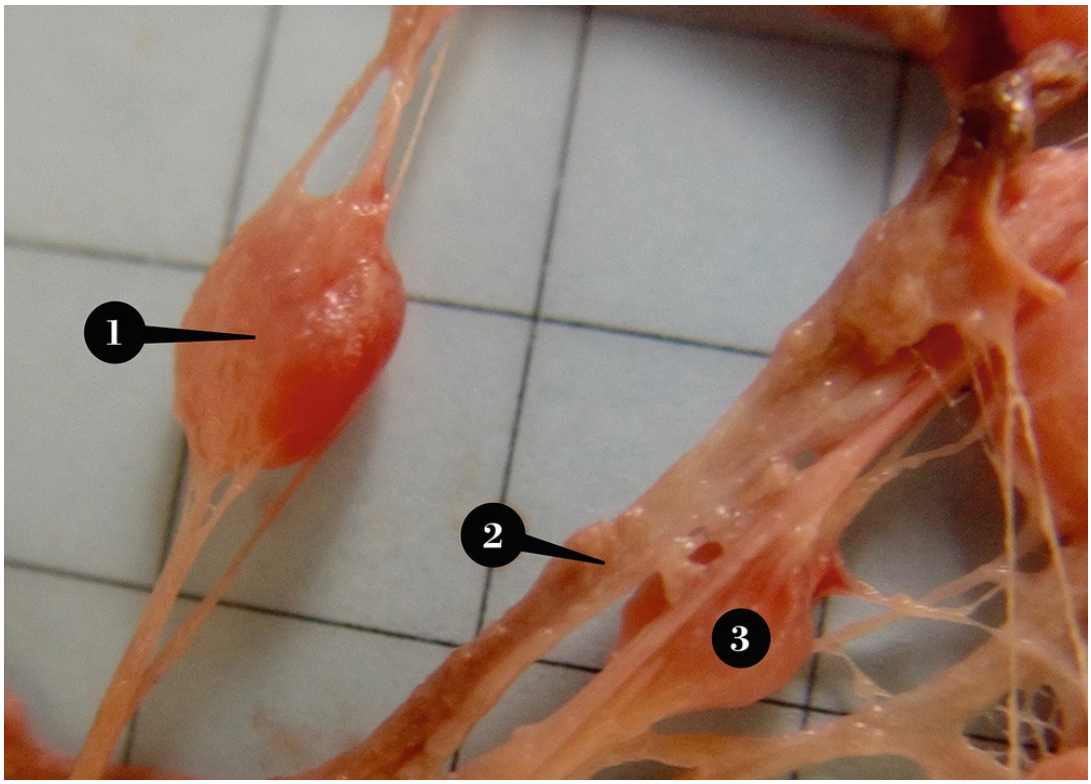

Fig. 4.9 The fragment of lymphatic apparatus of the axillary region. Figures 1 and 3 illustrate lymph nodes, and 2 illustrates the great vessel. The lymph node 1 has an elongated shape; the capsule is well-formed. The node is drained through newly formed vessels

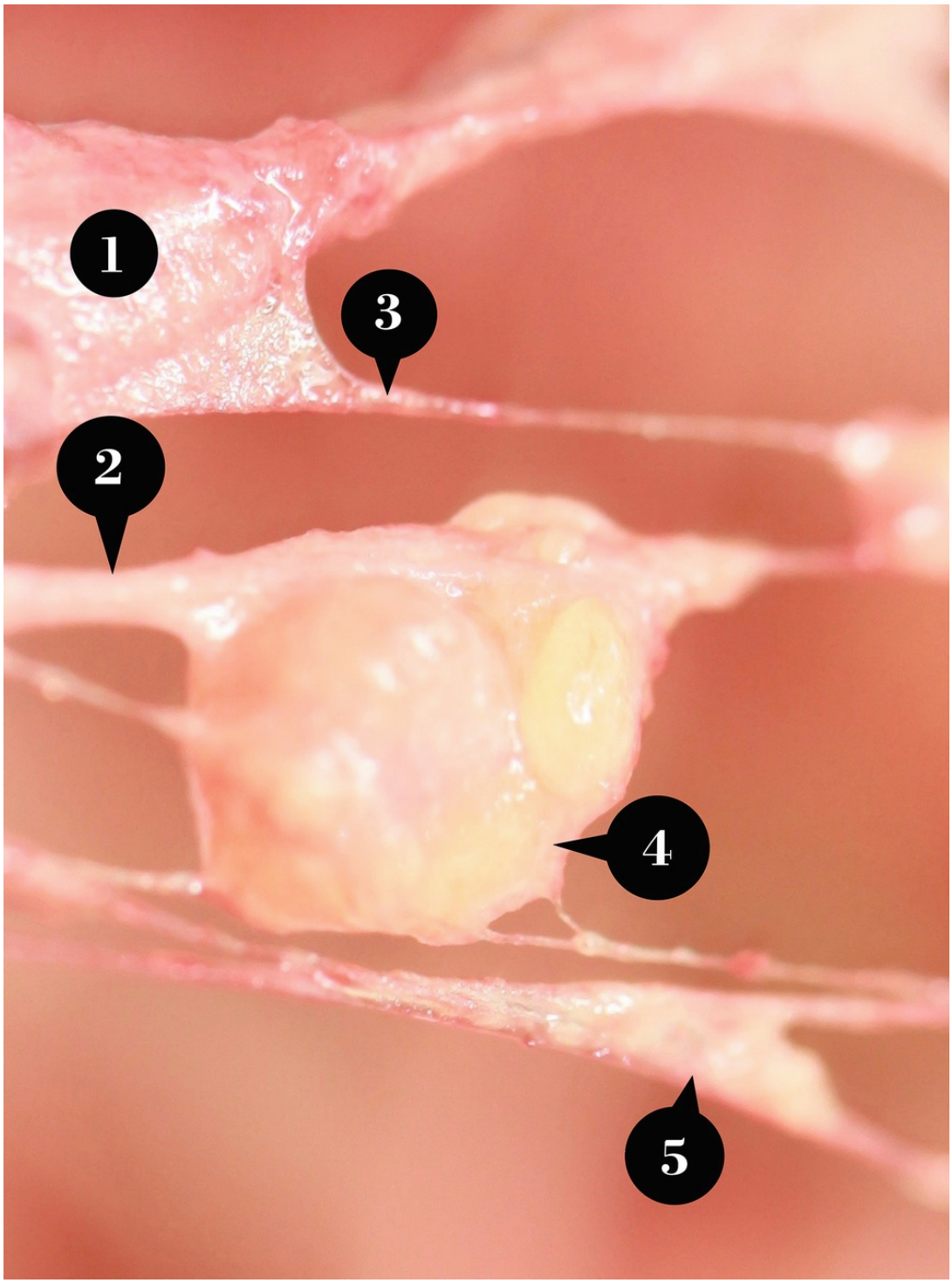

Fig. 4.10 The lymph node of the axillary region (4) with atypical lymphatic drainage and connection with the great vessel (1). Figures 2 and 5 illustrate the large lymphatic trunks, from which the smaller vessels emerge (3)

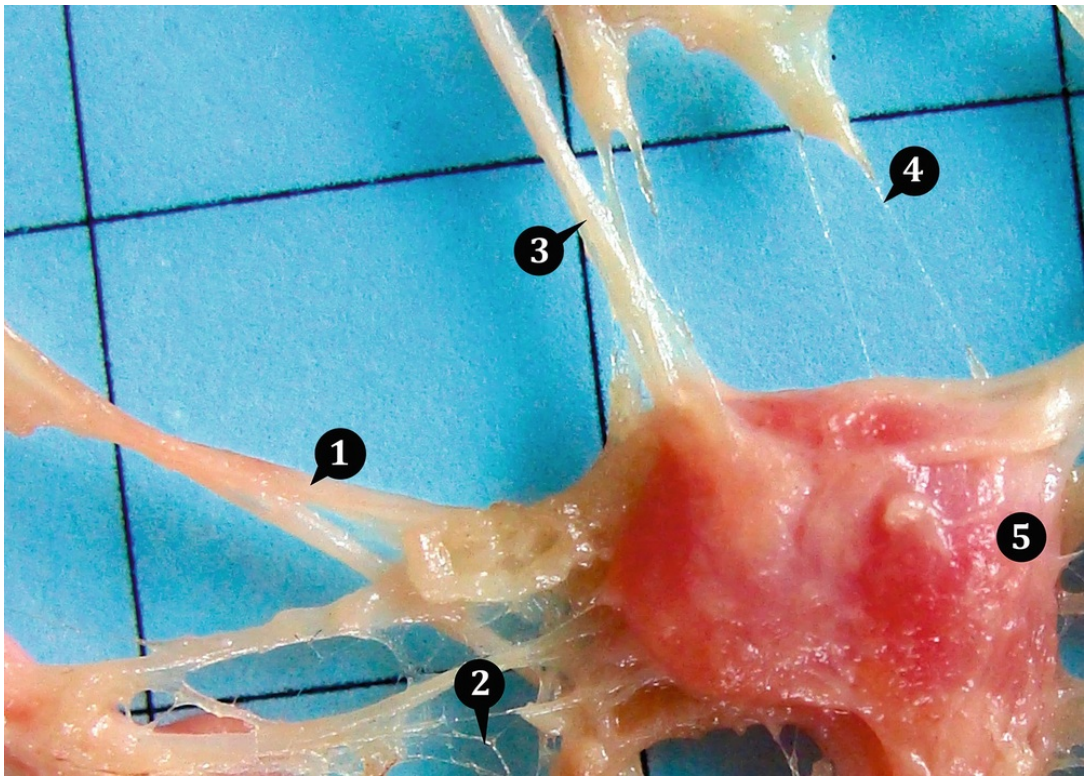

Fig. 4.11 The fragment of the lymph node (5) with a large number of vessels that penetrate the lymph node. Figures 1, 2, 3, and 4 illustrate the newly formed lymphatic vessels of different diameters. Near the capsule, there is a vascular conglomeration. The lymph node is inhomogeneous; sections of normal structure are interchanged with lipopexia

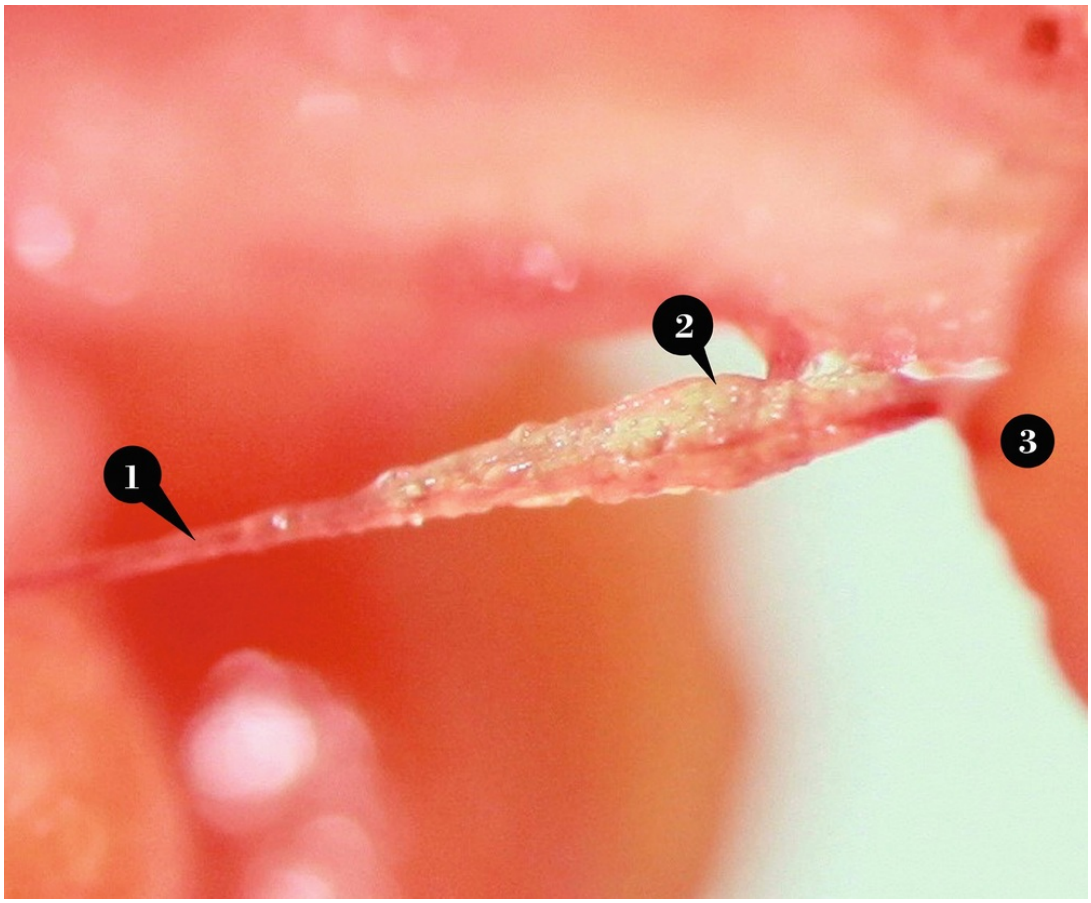

Fig. 4.12 The inflow lymphatic vessel, which is blocked by cancer cells (cancer lymphangitis). Figure 1 illustrates the inflow vessel, 2 section of the vessel filled with cancer metastases, and 3 fragment of the lymph node

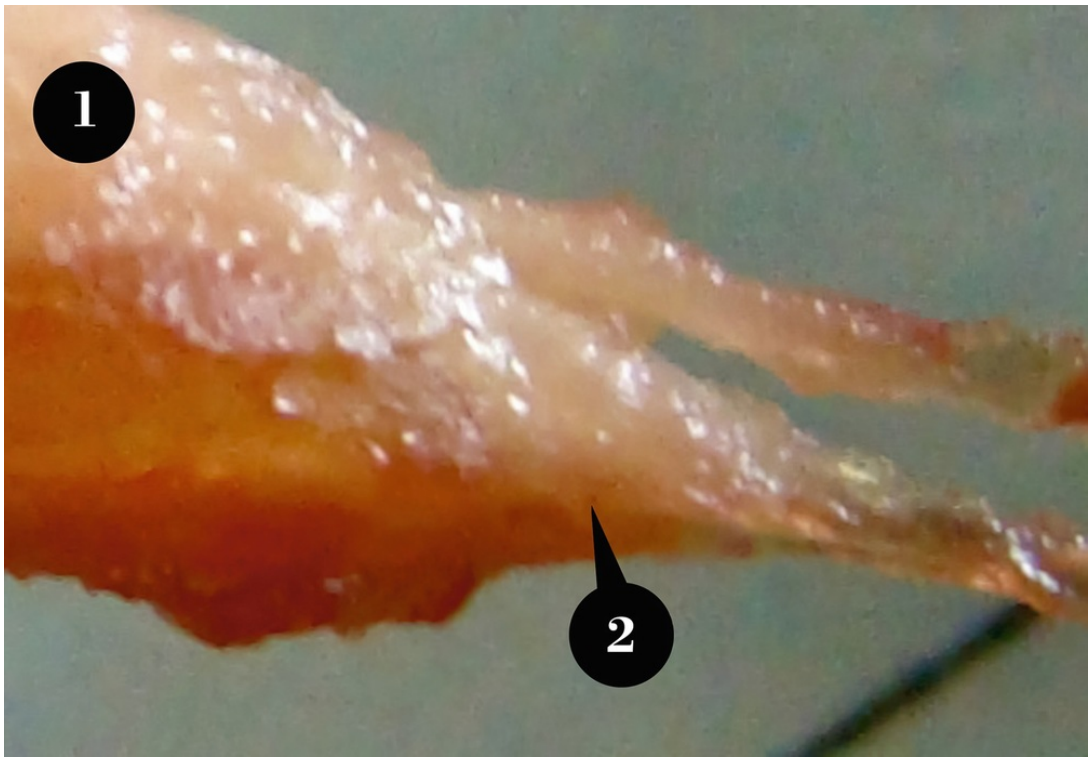

Fig. 4.13 Total blocking with cancer cells of lymph node (1) and lymphatic vessels (2). The ratio of the vessel in the capsule region and at a distance of 10 mm from it is 3:1. There is a conical enlargement of lymphatic vessel at the base located on the lymph node capsule

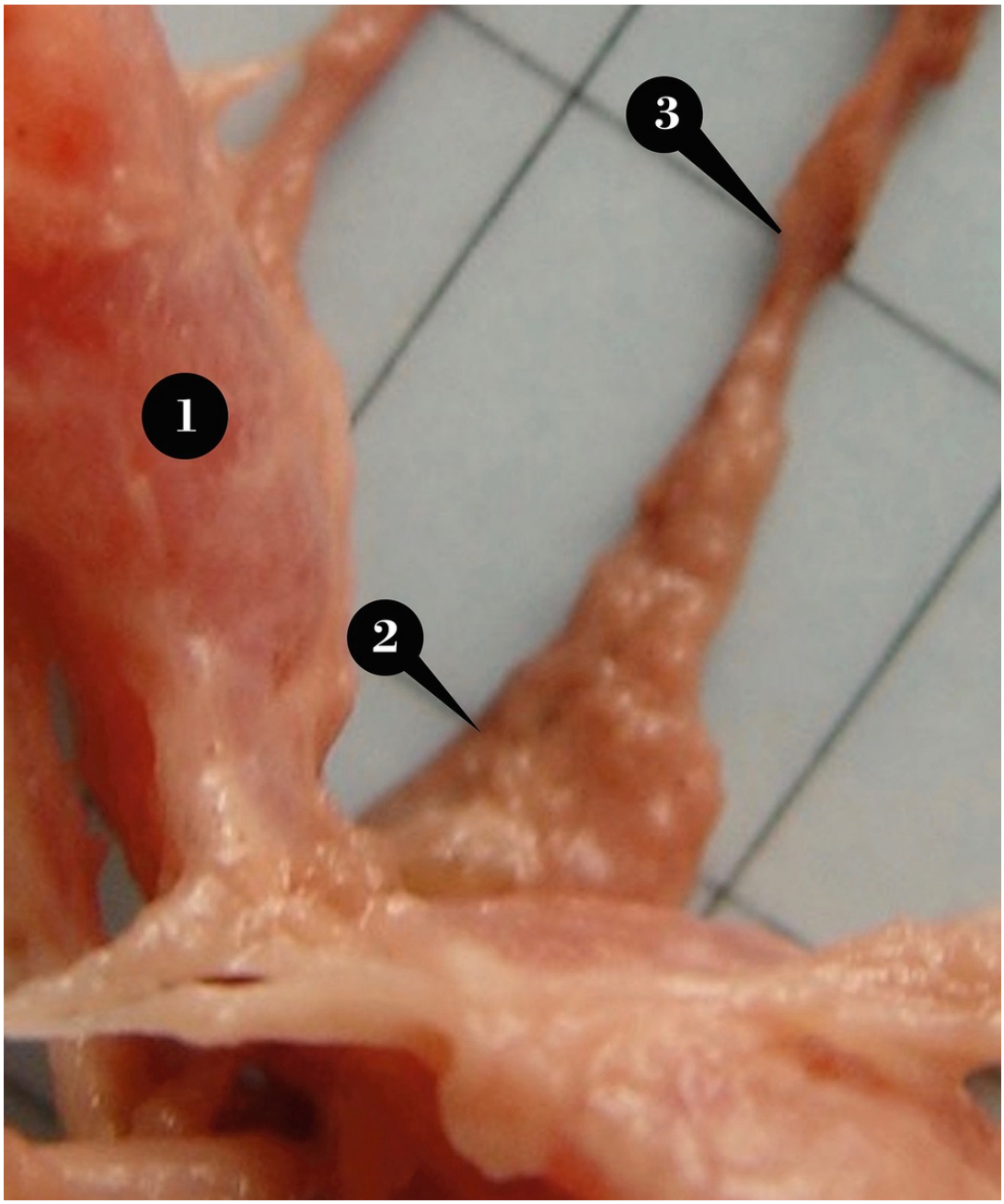

Fig. 4.14 The fragment of lymphatic drainage system in cancer with overall affection of lymph node. Figure 1 illustrates the lymph node and 2 inflow lymphatic vessel which is filled with cancer cells (lymphangitis) for more than 15 mm. The diameter in regions 2 and 3 has a ratio of 5

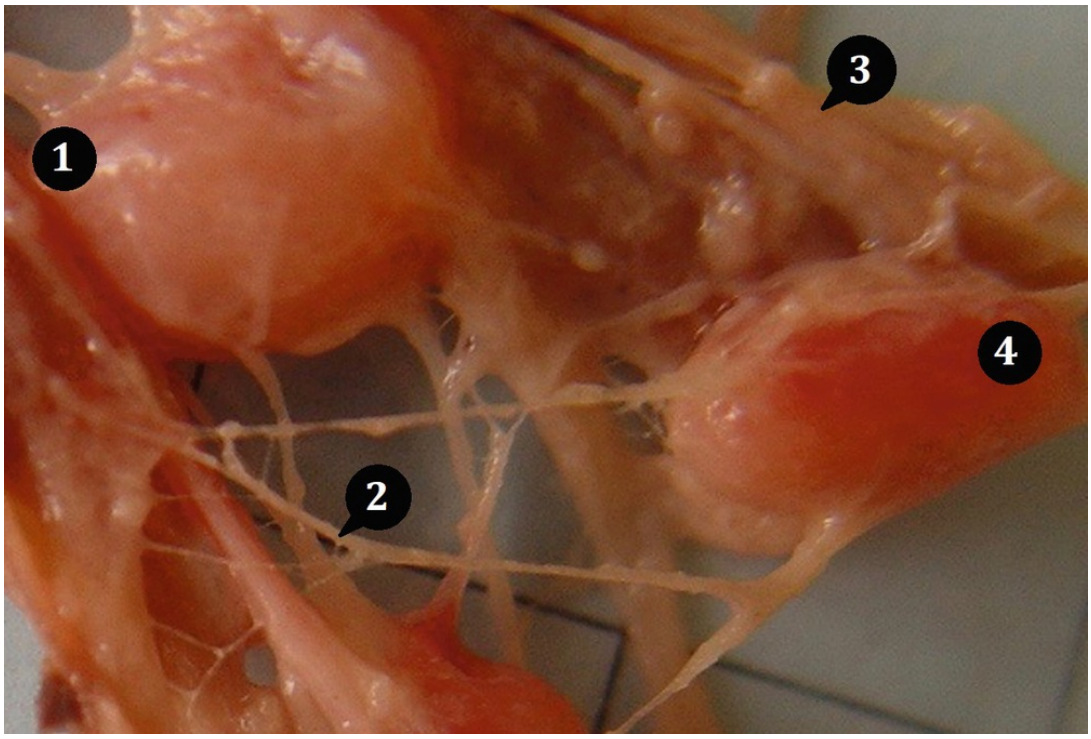

Fig. 4.15 The fragment of the axillary lymphatic collector in breast cancer. Figures 1 and 4 illustrate the lymph nodes that provide a lymphatic drainage of this zone. Figures 2 and 3 illustrate the vascular component: 2 newly formed lymphatic capillaries and 3 the great vessels with tubercles (tertiary lymphatic organs)

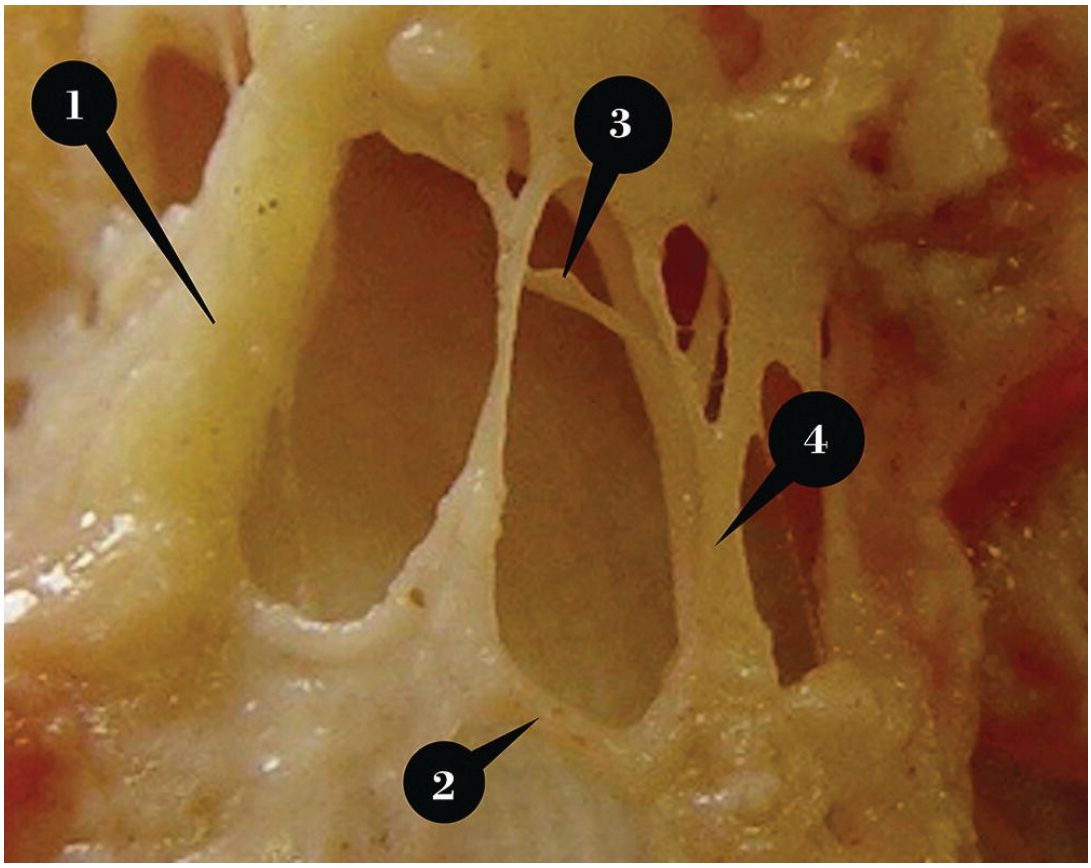

Fig. 4.16 Drainage-uptake lymphatic bed. Figure 1 illustrates the great vessel, 2,2,4-lymphatic vessels, and collaterals. The vessels have a loop (2)

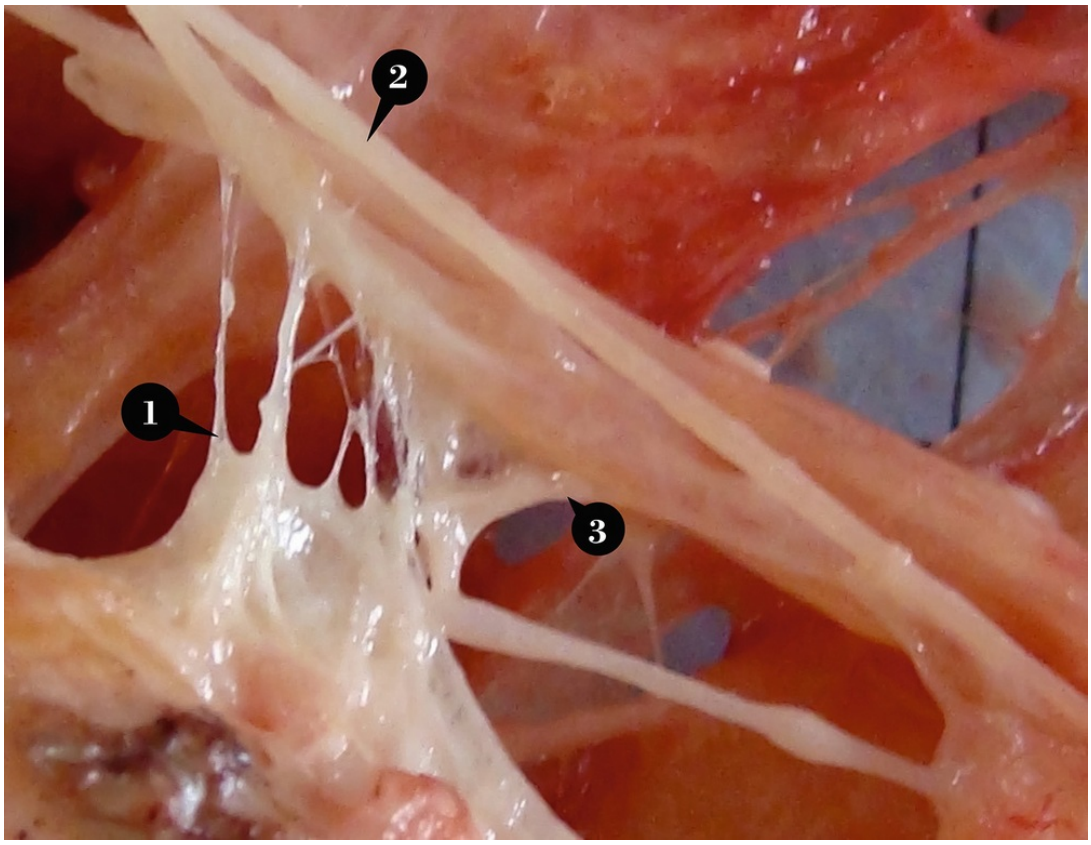

Fig. 4.17 The great lymphatic vessels (2,3) provide an active lymph transfer. Figure 1 illustrates newly formed lymphatic vessels which connect collectors with each other

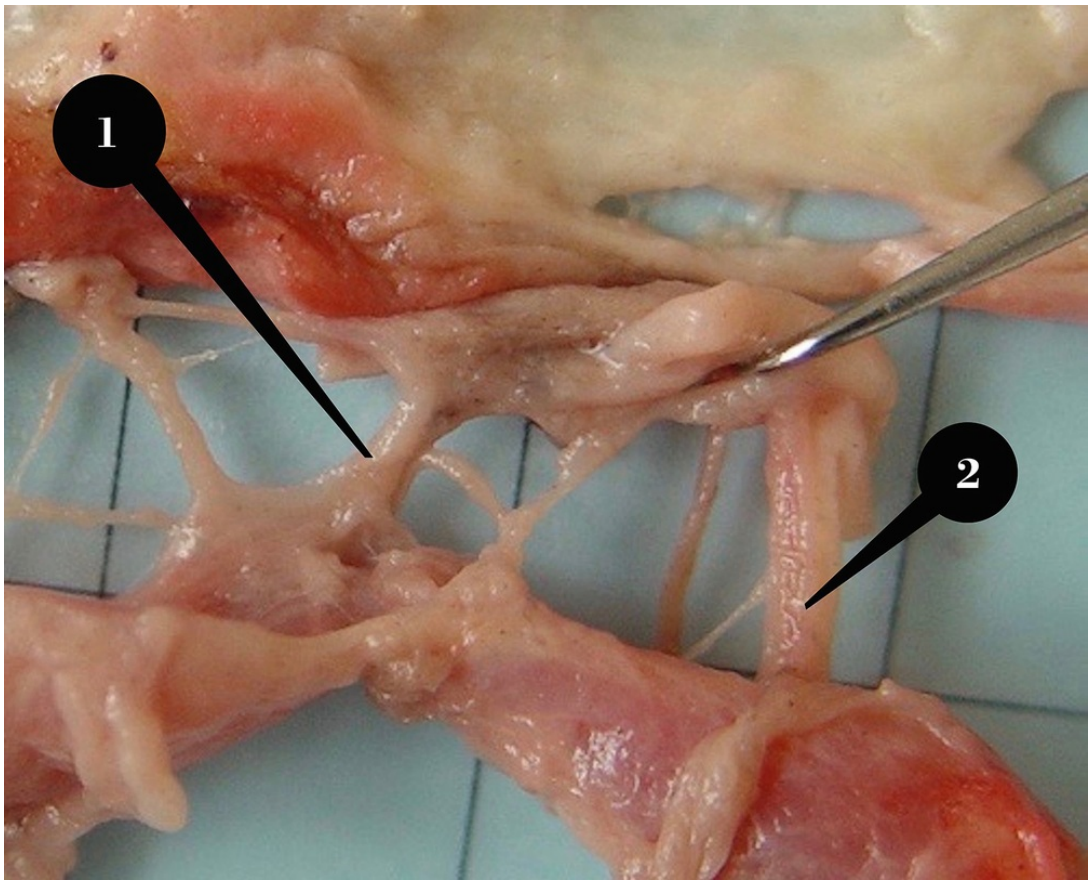

Fig. 4.18 Well-formed vessels (1,2) providing lymph circulation of the regional basin. The diameter of the vessels is in large excess over the norm

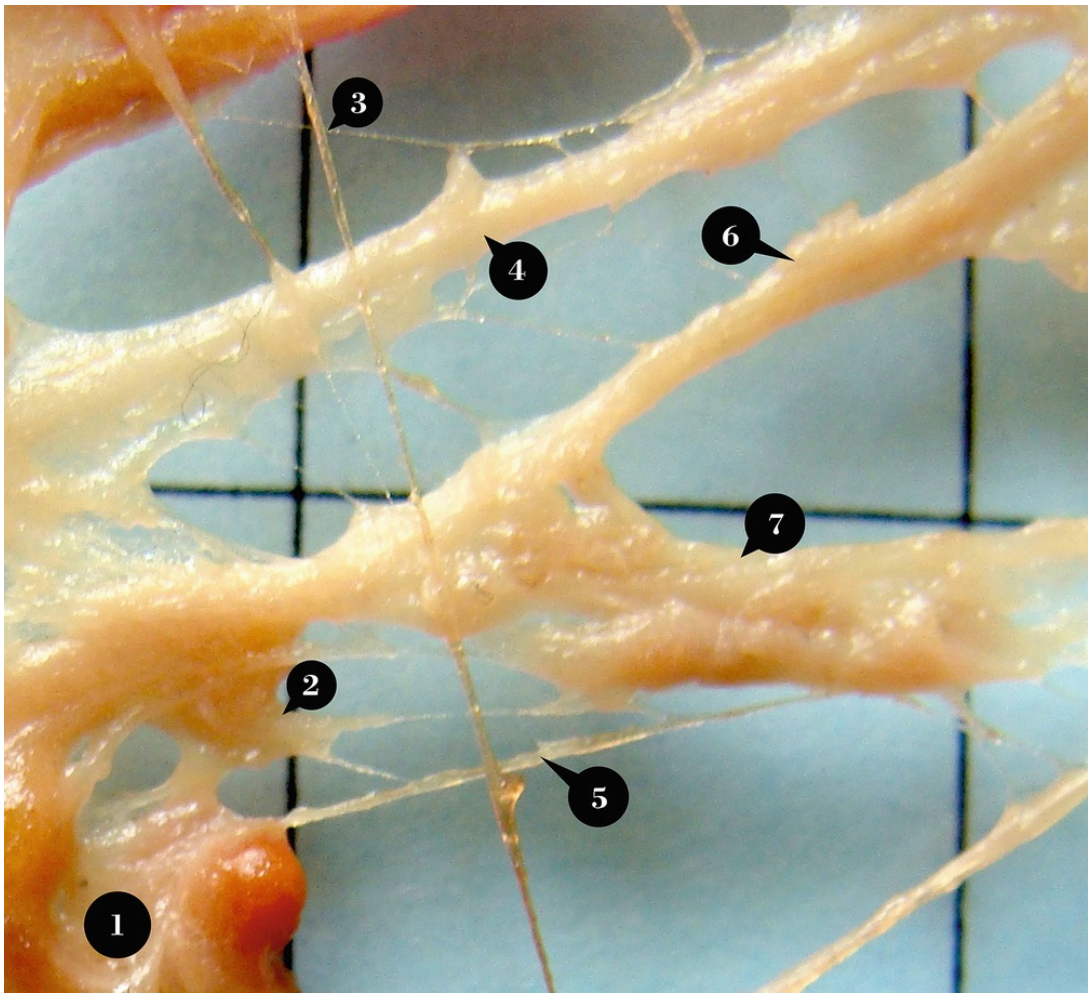

Fig. 4.19 The fragment of lymphatic bed of the axillary region in cancer with metastases. Figure 1 illustrates a portion of the lymph node, 2 lymphatic cistern where several large and small vessels are interfused, and 3 transient vessel providing interzonal drainage, and 4, 5, and 6 illustrate lymphatic vessels of various diameter and functions

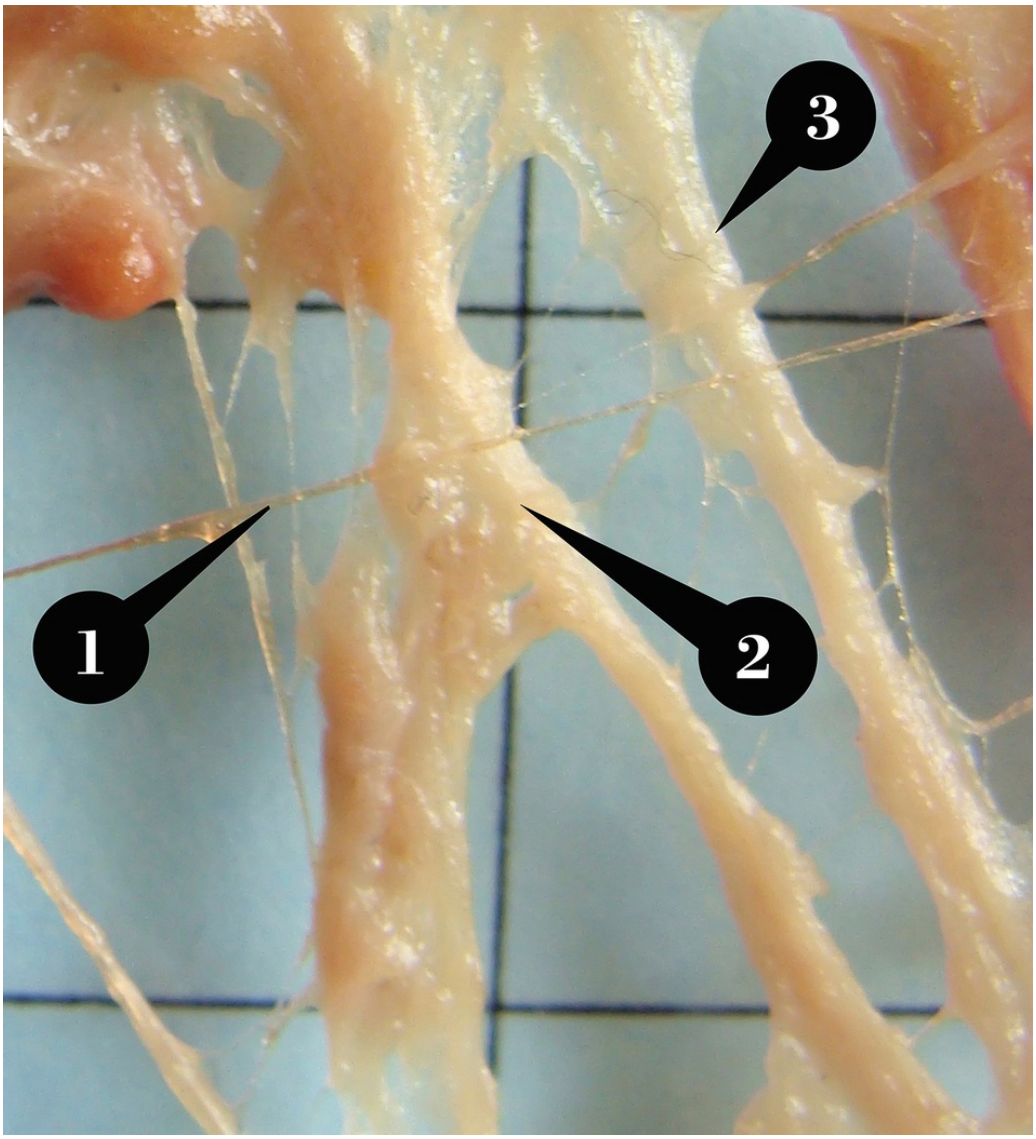

Fig. 4.20 Isolated lymphatic vessels of the axillary region (1,2,3). The vessels have a different degree of intensity. Figure 1 illustrates newly formed lymphatic vessels, 2 branching of lymphatic vessel into two (the left one has uneven contours with an adjacent vessel), and 3 well-formed cylinder-shaped lymphatic vessel

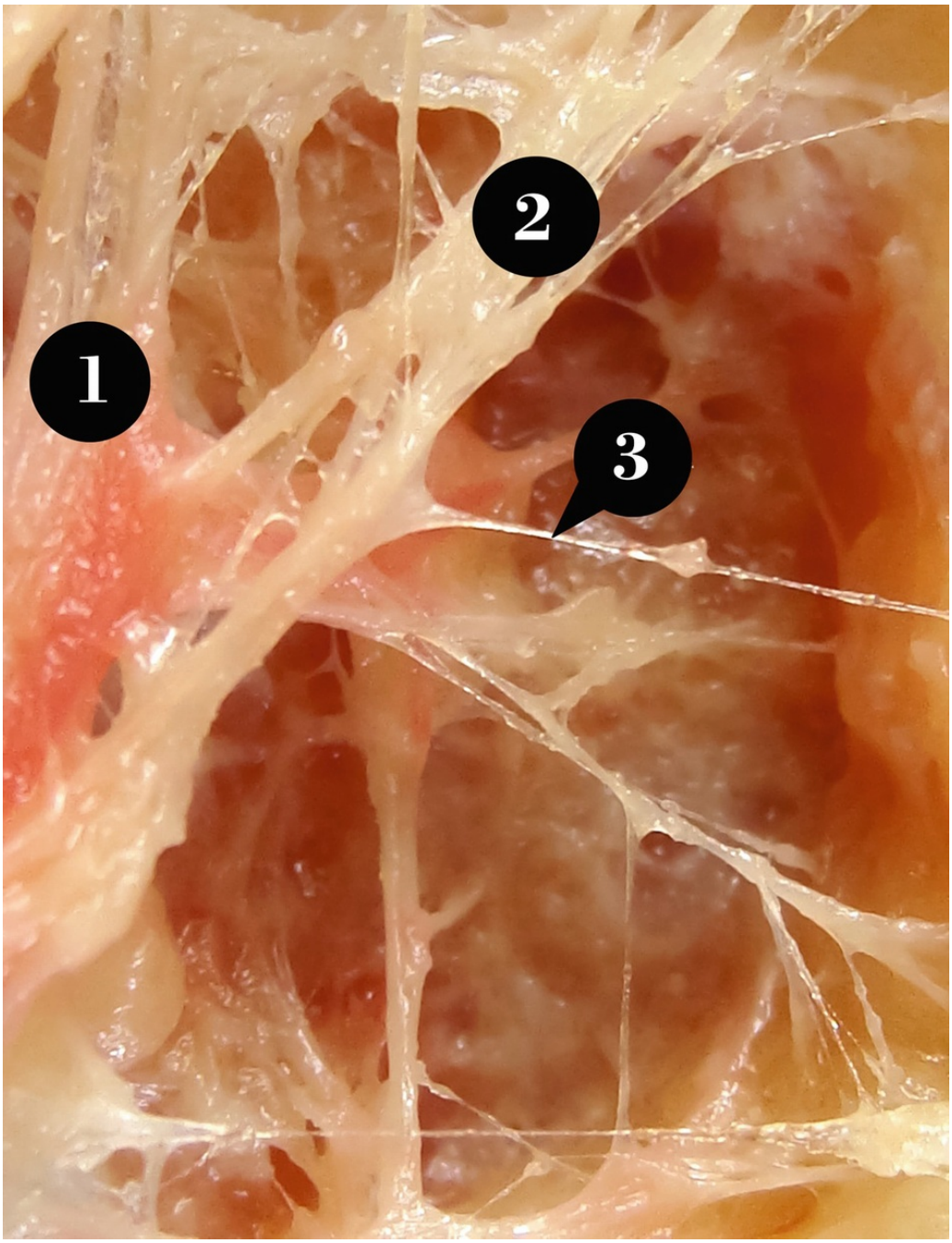

Fig. 4.21 The great lymphatic vessels (1,2) of the axillary region and multiple newly formed lymphatic vessels with a large number of collaterals

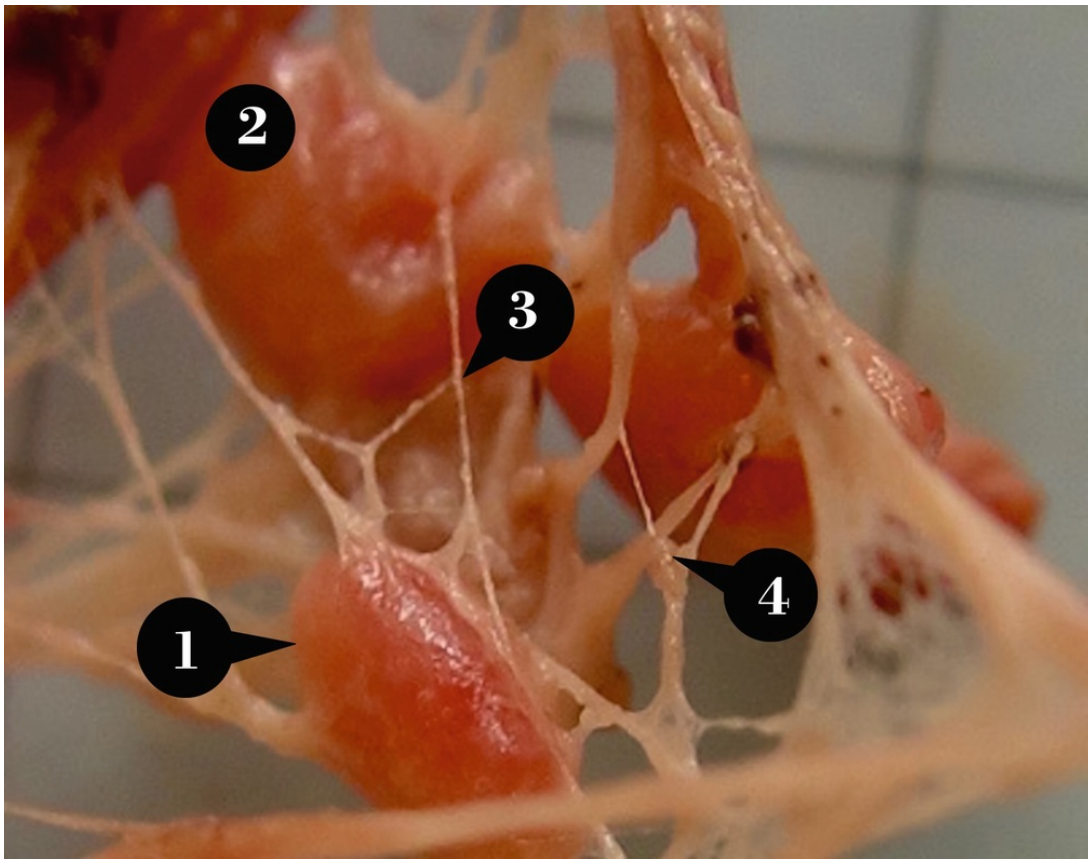

Fig. 4.22 A group of lymph nodes (1, 2) connected by newly formed vessels (3,4) of various diameters providing lymphodynamics and regional lymph dynamic balance

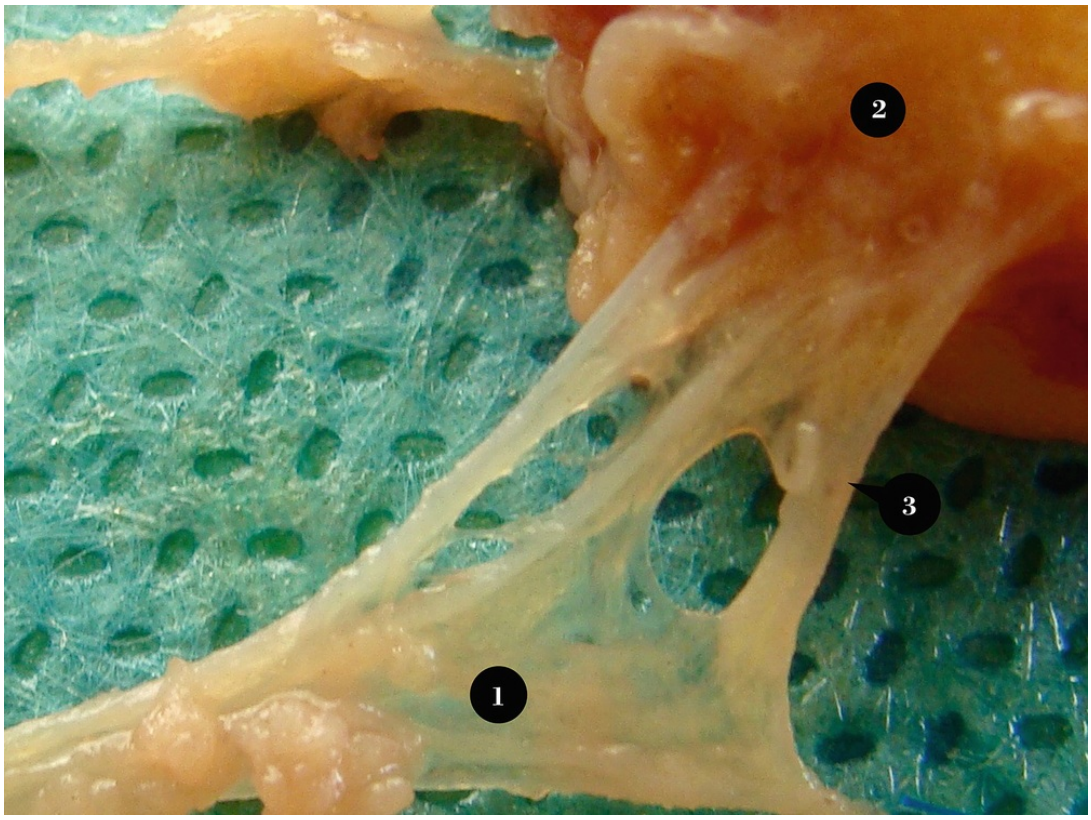

Fig. 4.23 The fragment of microvascular lymphatic bed in breast cancer. Figure 1 illustrates the great lymphatic vessels and 2 the lymph node and microcirculation vessels (3). Microsurgical dissection, an enlarged photo to x 6

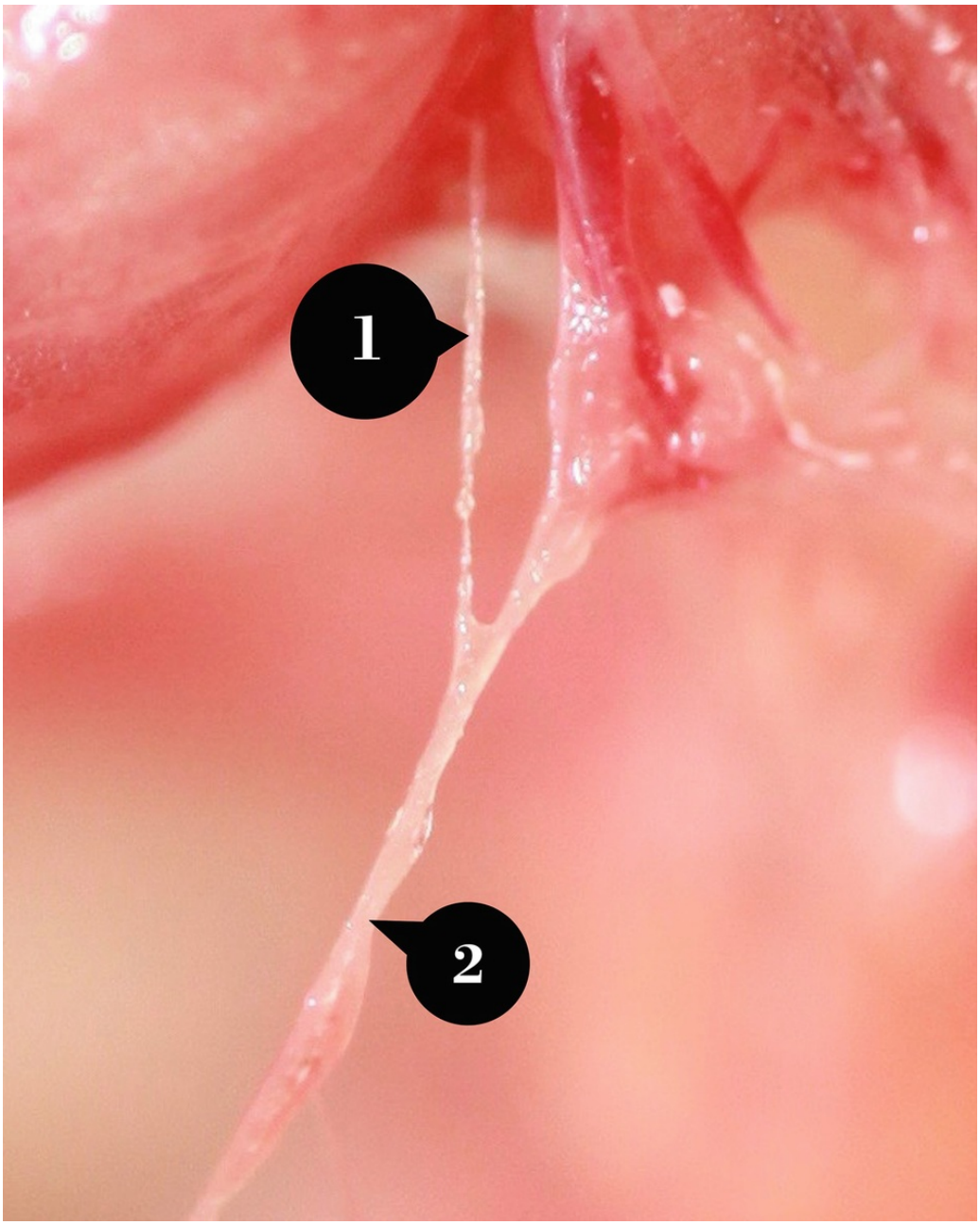

Fig. 4.24 The newly formed thinnest vessels surrounding the lymph node. Figure 1 illustrates the great vessel, and it has distentions and constrictions along its length, and 2 – the newly formed lymphatic vessel flowing toward the node. This vessel has uneven contours, combining constrictions and distentions

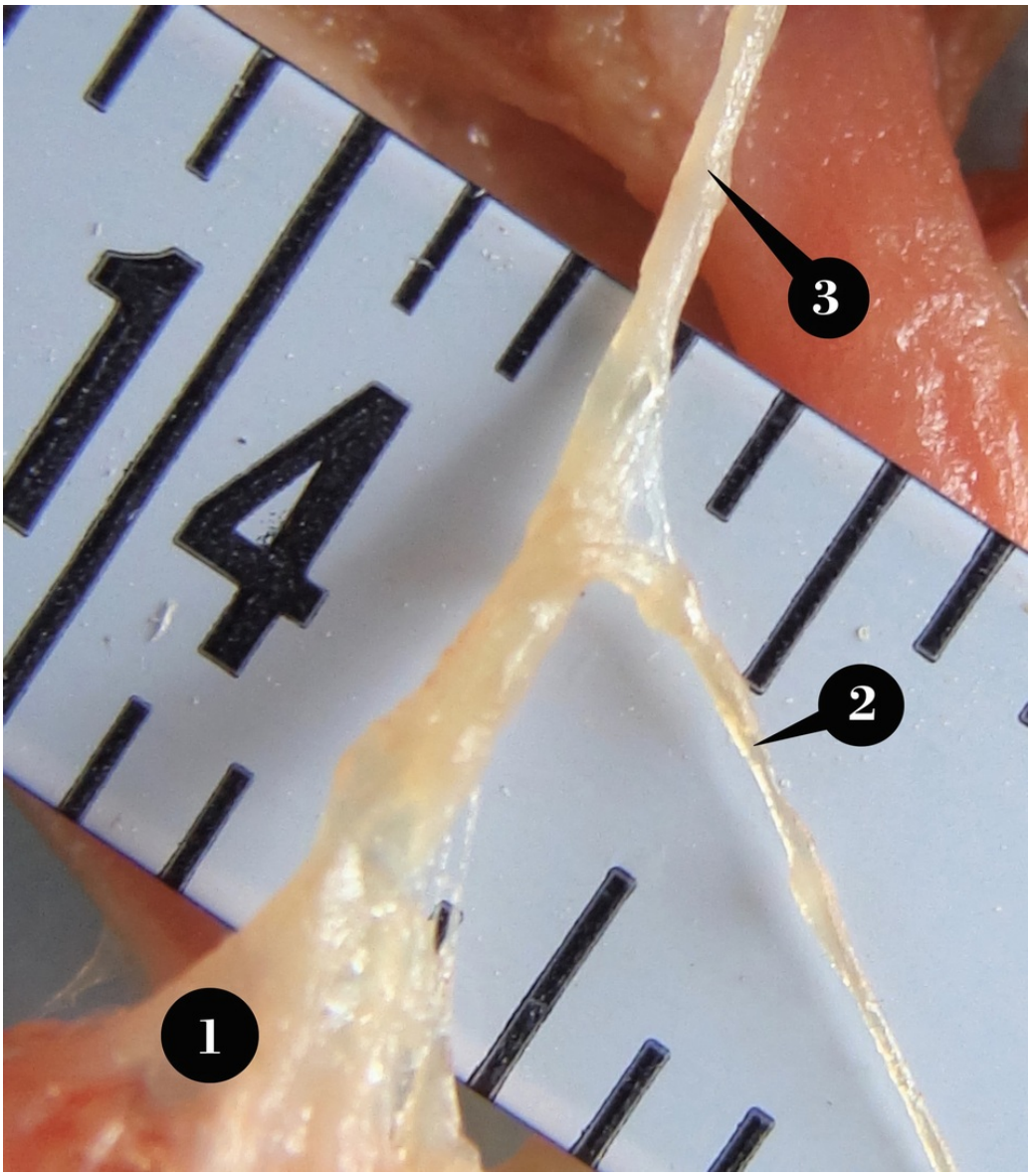

Fig. 4.25 The inflow lymphatic vessel is placed on the ruler. Figure 1 illustrates lymphonodular transition with the base expansion on the capsule, 3 the main fragment of the vessel, and 2 newly formed lymphatic vessel flowing toward the node

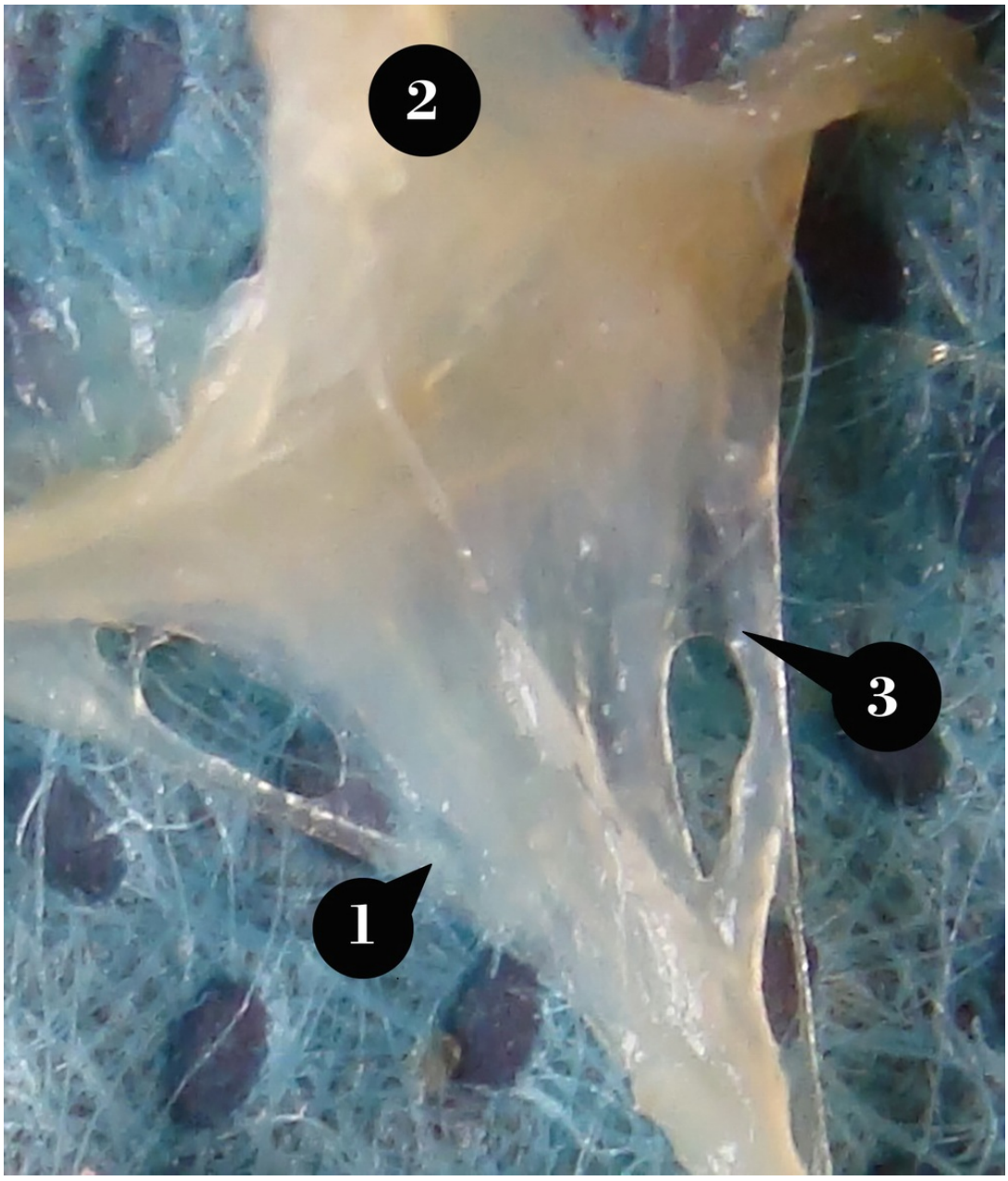

Fig. 4.26 The fragment of the lymph node capsule (2) and newly formed lymphatic vessels (1,3). The complex was isolated by microsurgical dissection, an enlarged photo to x 6

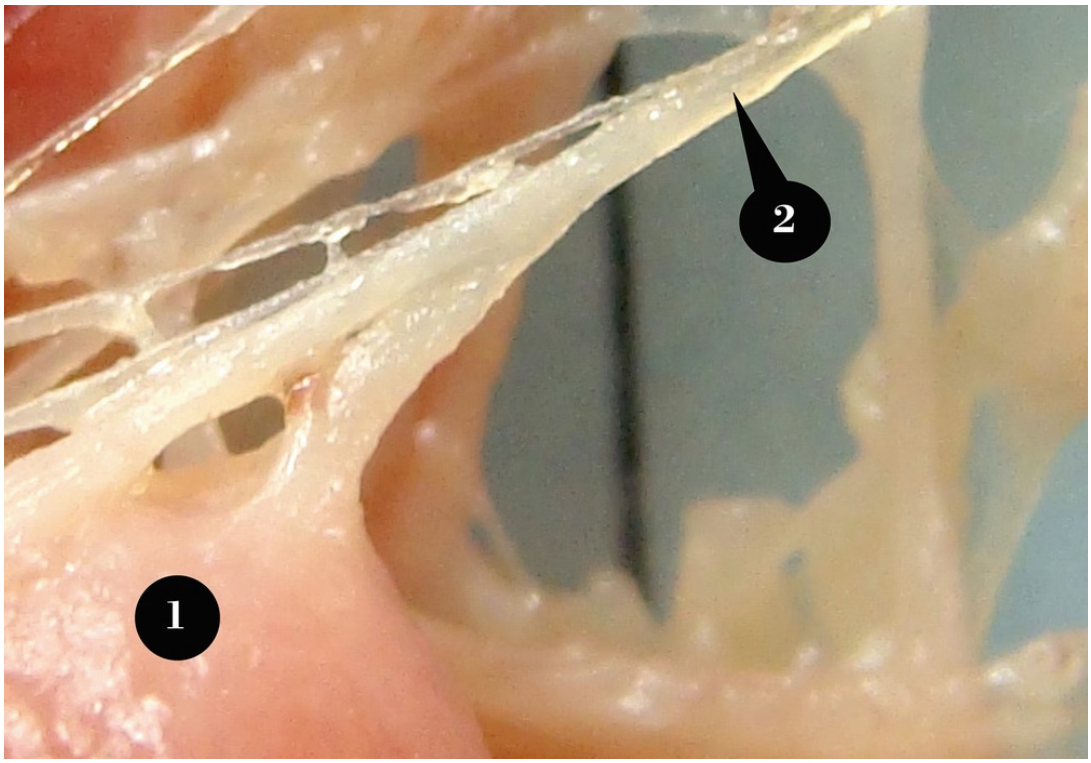

Fig. 4.27 The fragment of the lymph node (1) and vascular component (2). Lymphatic vessels have a well-formed structure; newly formed vessels have formed collaterals

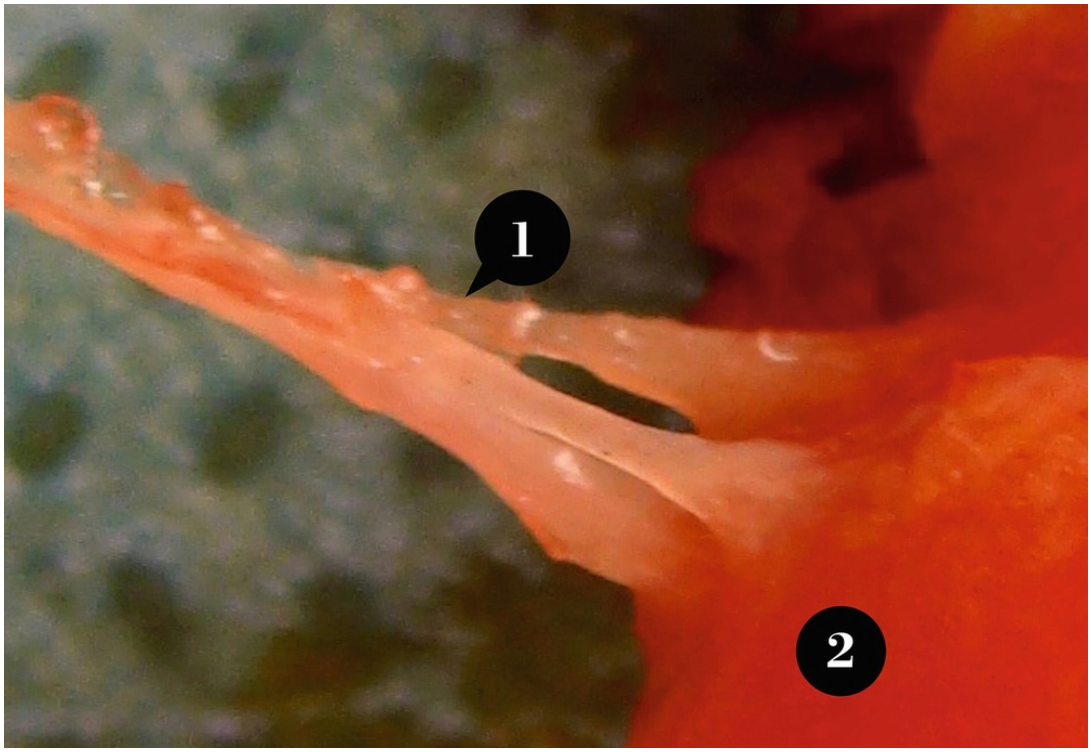

Fig. 4.28 The lymph node vessels are isolated by microsurgical dissection. The scattered type of afferent lymphatic vessels (1), the part of newly formed vessels, 2-the lymph node

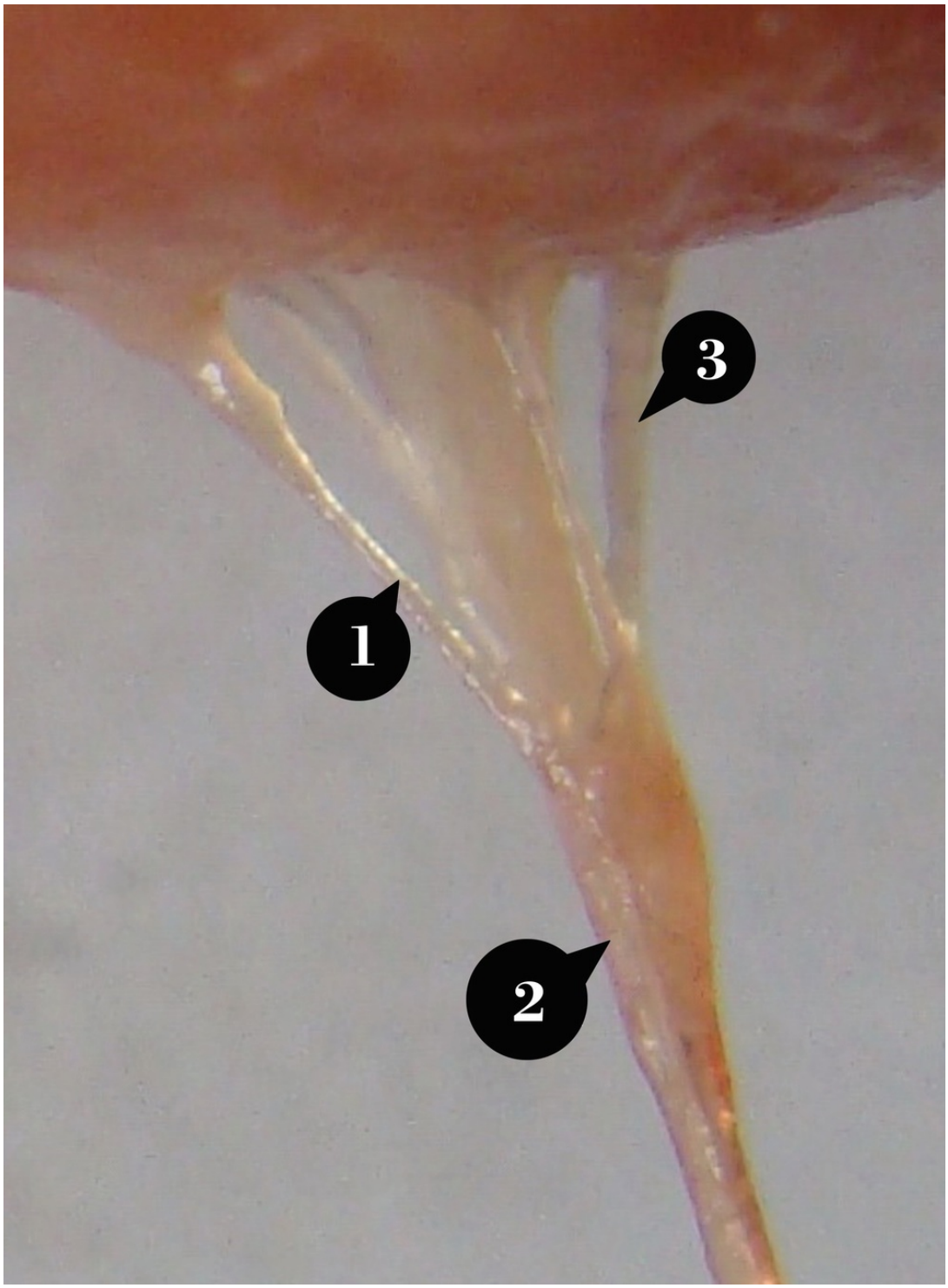

Fig. 4.29 The scattered type of afferent lymphatic vessel. Figure 1 illustrates the newly formed lymphatic vessel, 2 the great vessel, and 3 branch lymphatic vessel

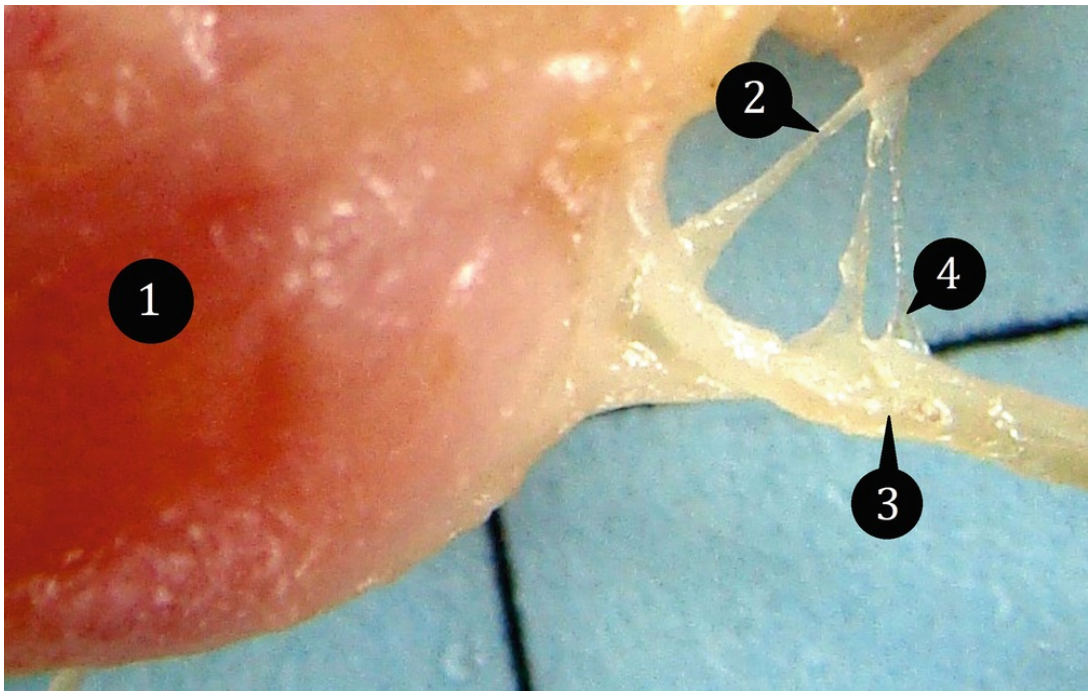

Fig. 4.30 The fragment of lymphonodular transition . Figure 1 illustrates a part of the lymph node, and 2 and 3 illustrate inflow vessels which anastomose with each other by newly formed lymphatic vessels (4)

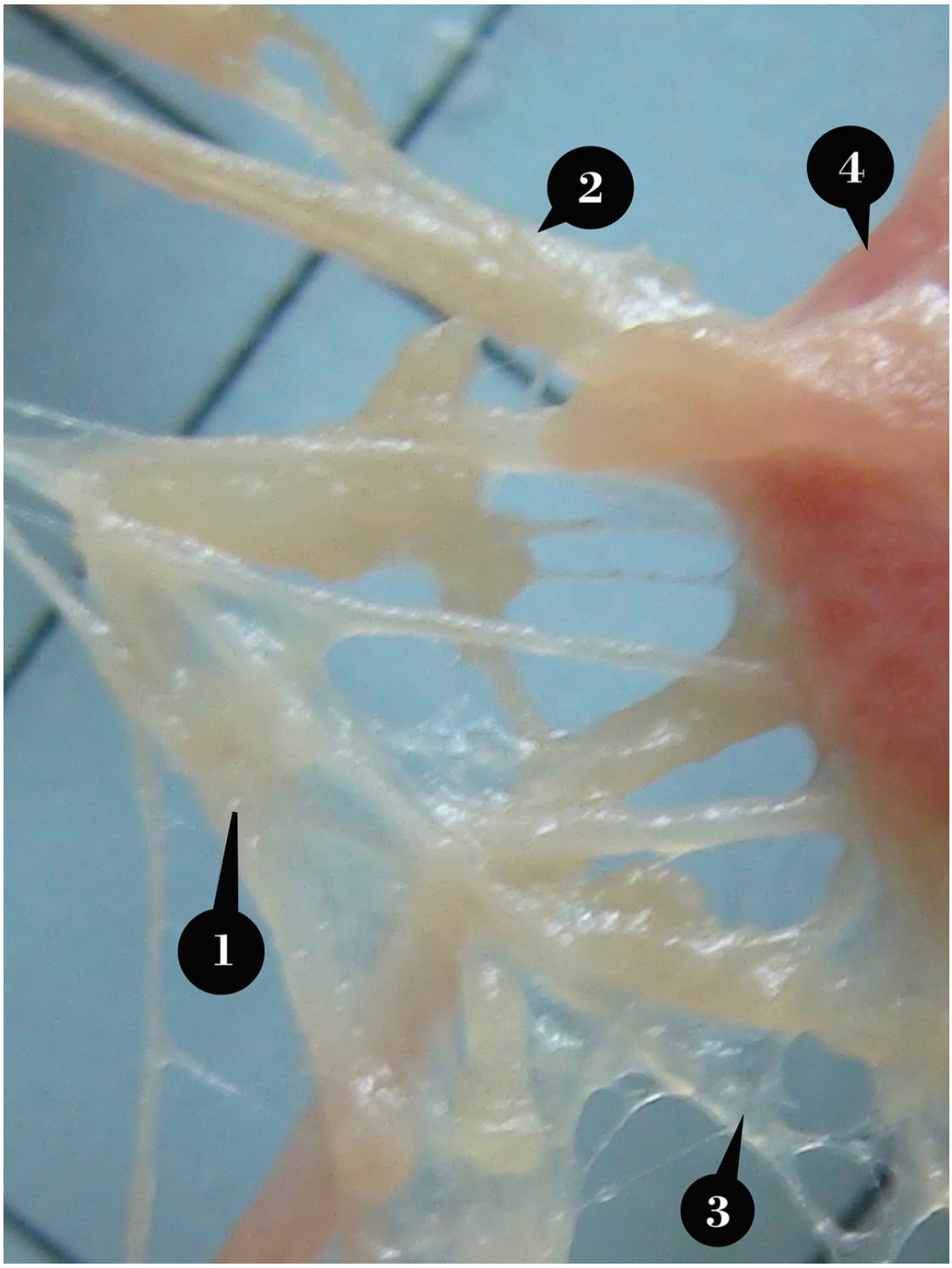

Fig. 4.31 A newly formed vascular bed (1, 3) surrounds the lymph node (4). 2 well-formed lymphatic vessel. This clinical pattern is characteristic for the sentinel lymph node in cancer (about 10 microcirculation vessels interconnect with a small fragment of the lymph node)

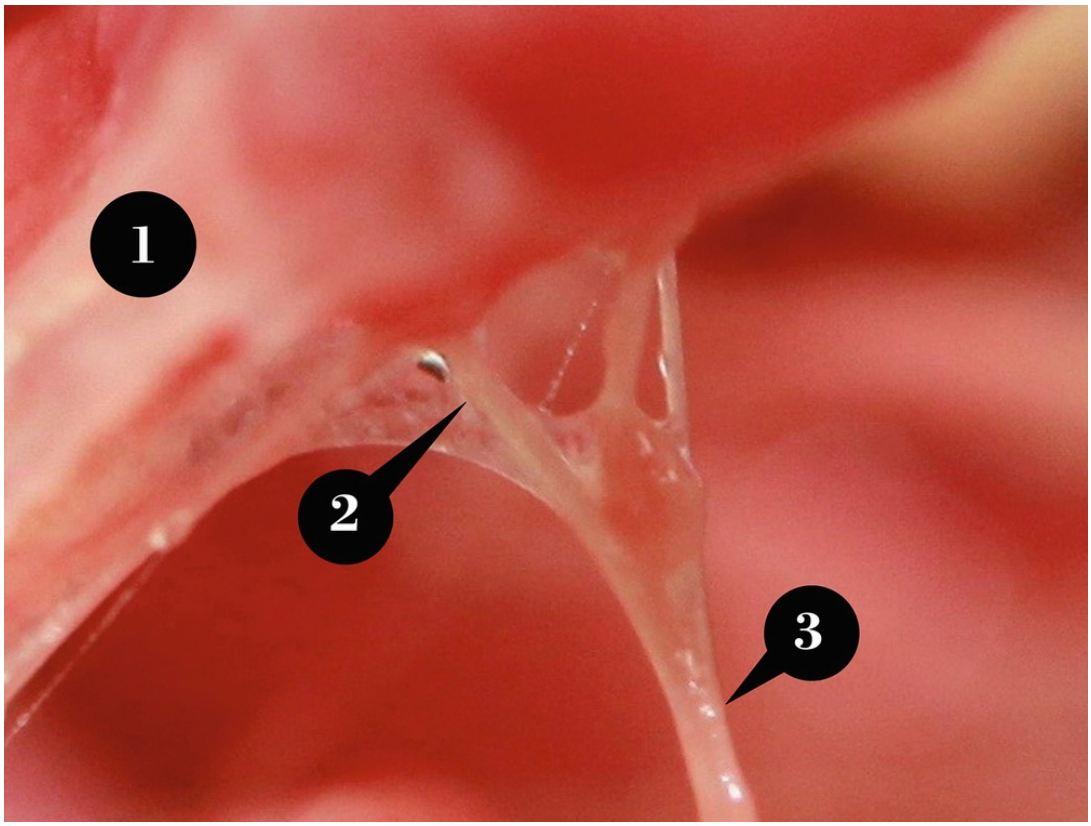

Fig. 4.32 The area of lymphonodular transition (2) bordering the connective tissue elements (1) fixing the node. Figure 3 illustrates the great lymphatic vessel, which is formed by adherence of several smaller vessels. There is a lymphoid formation (tertiary lymphoid organ) in the zone of trifurcation

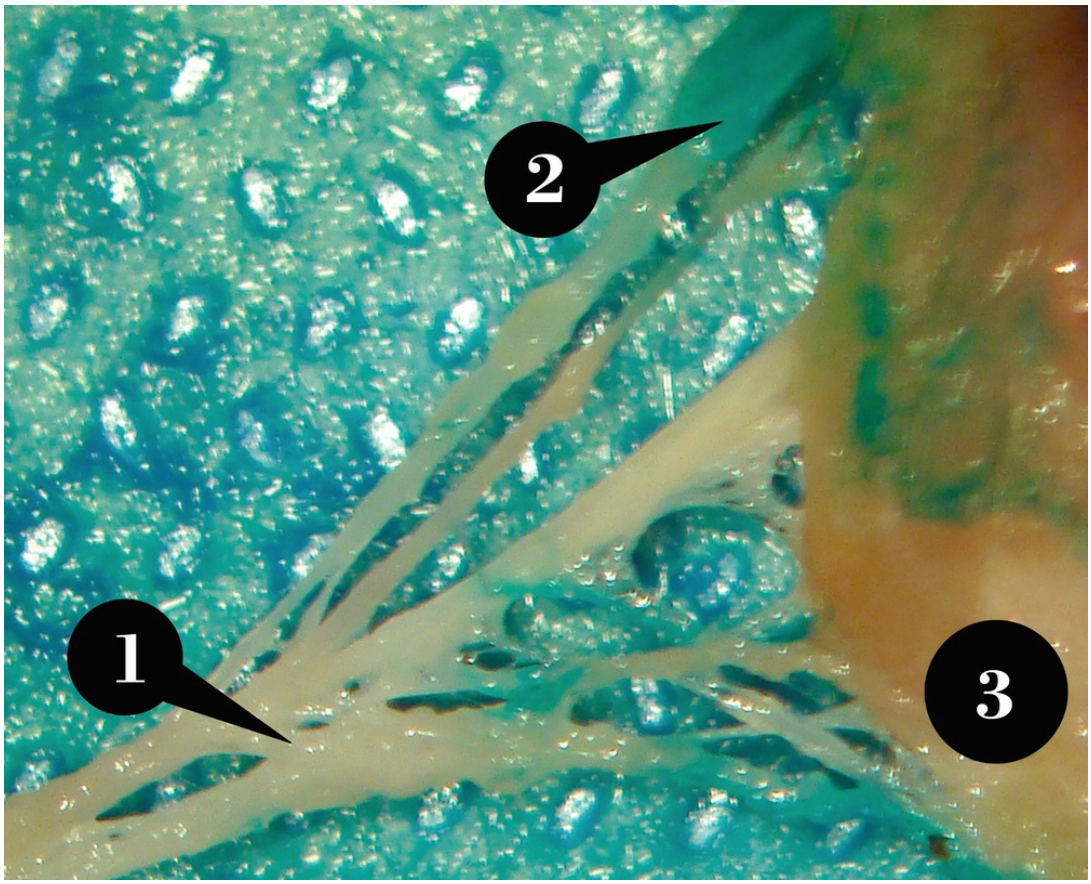

Fig. 4.33 Numerous lymphatic vessels (1,2) in the region of their adherence to the node (3). The contours of the vessels differ in variety; in some places constrictions are interchanged with distentions

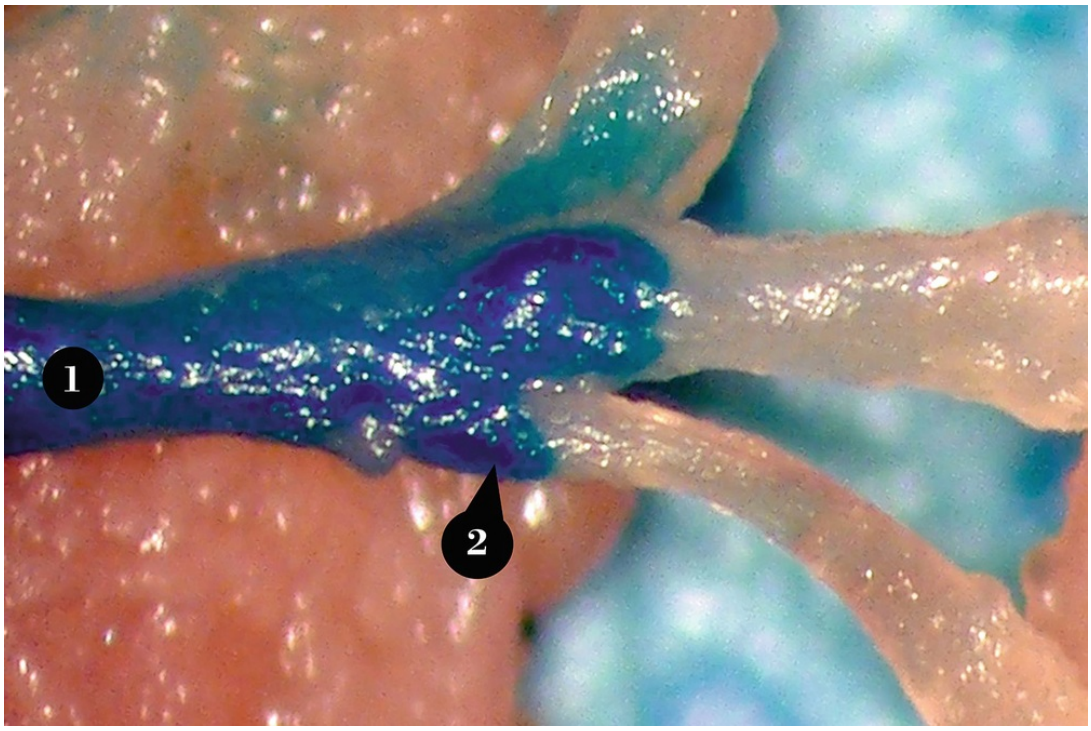

Fig. 4.34 Retrograde color lymphography. Figure 1 illustrates the great vessel; 2 contrast process is stopped due to the closing of valves

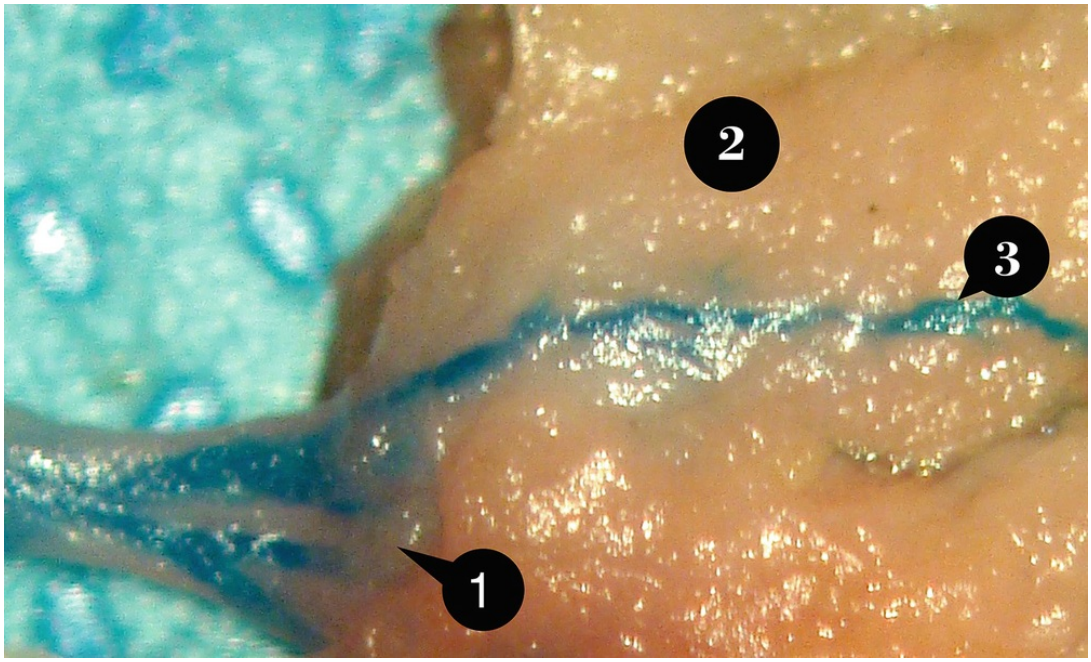

Fig. 4.35 Color lymphography of inflow vessels of the lymph node (2). The inflow lymphatic vessel is filled with the contrasting mass. Figure 1 illustrates a symptom of amputation: one of four branches of the vessel was

contrasted (3); it may provide evidence of a metastatic lesion of the lymph node segment

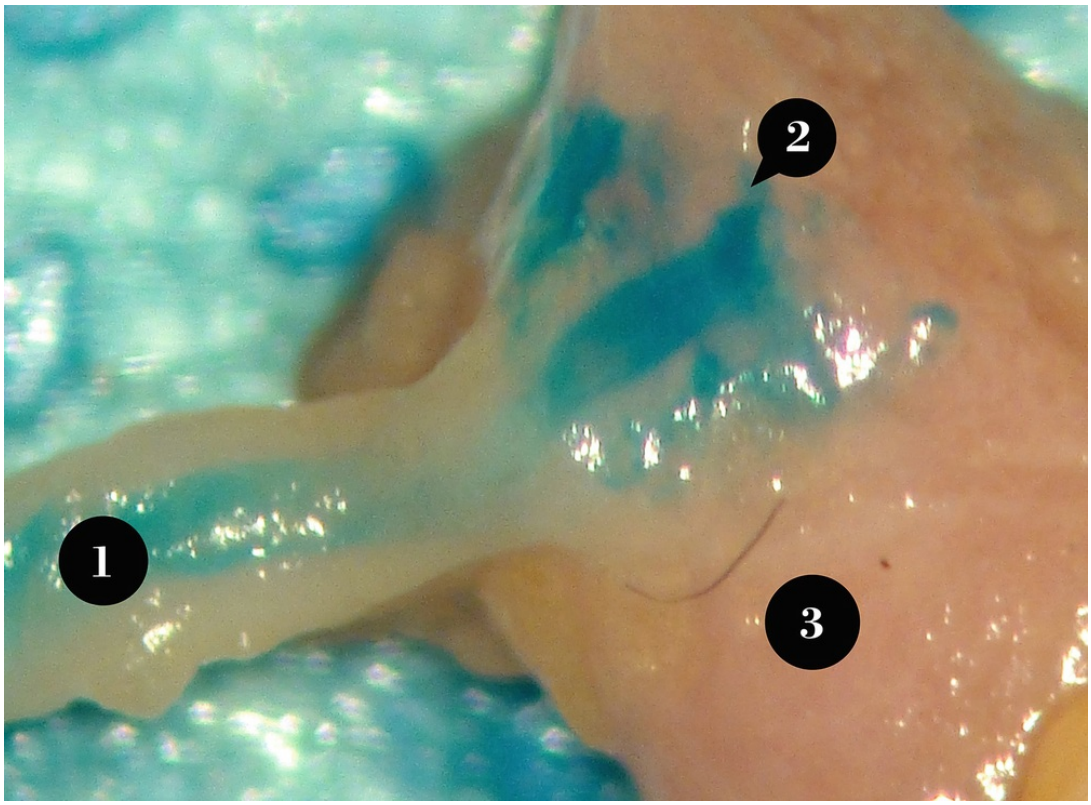

Fig. 4.36 The lymphatic vessel (1) and a part of vessels (3) of the lymph node (2) are contrasted. Contrast is seen badly enough due to the mass of subcutaneous tissue

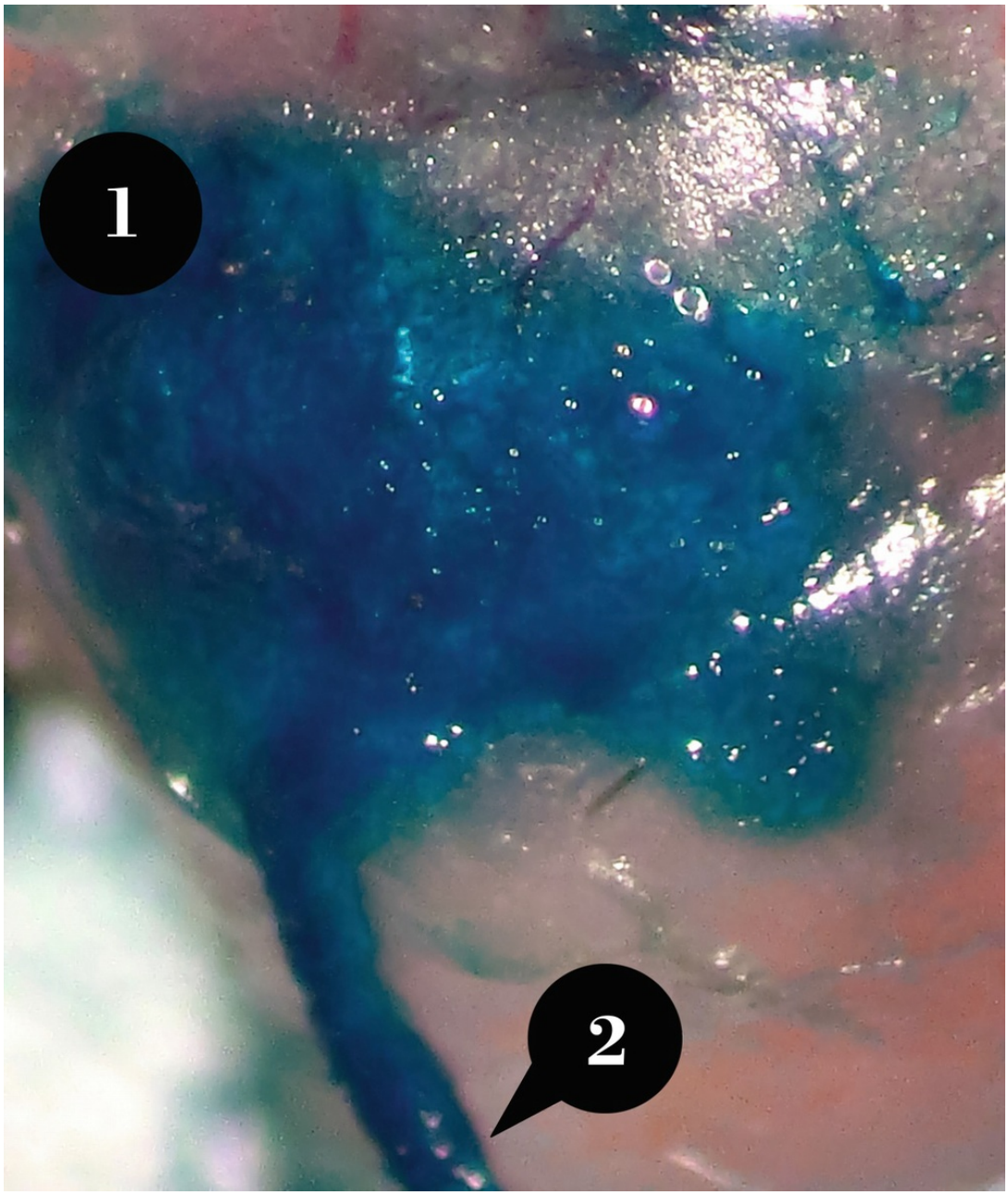

Fig. 4.37 Lymphogram . The great vessel is well-formed; the diameter is constant along its entire length (2). There is a homogeneous staining of the lymph node sinus

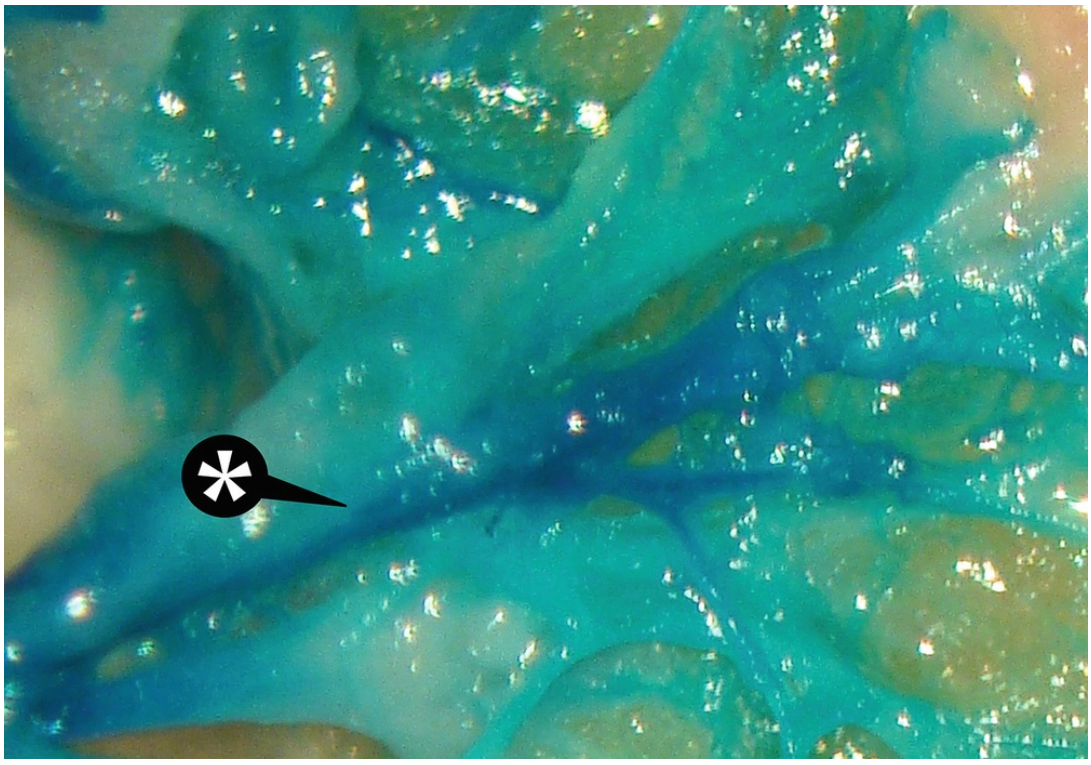

Fig. 4.38 Chromolymphography of blood vessels in axillary fat in cancer. The vessels are correctly organized (∗); there are glomeruli in the area of vessels' division. Lymphatic vessels are surrounded by a well-formed connective tissue membrane

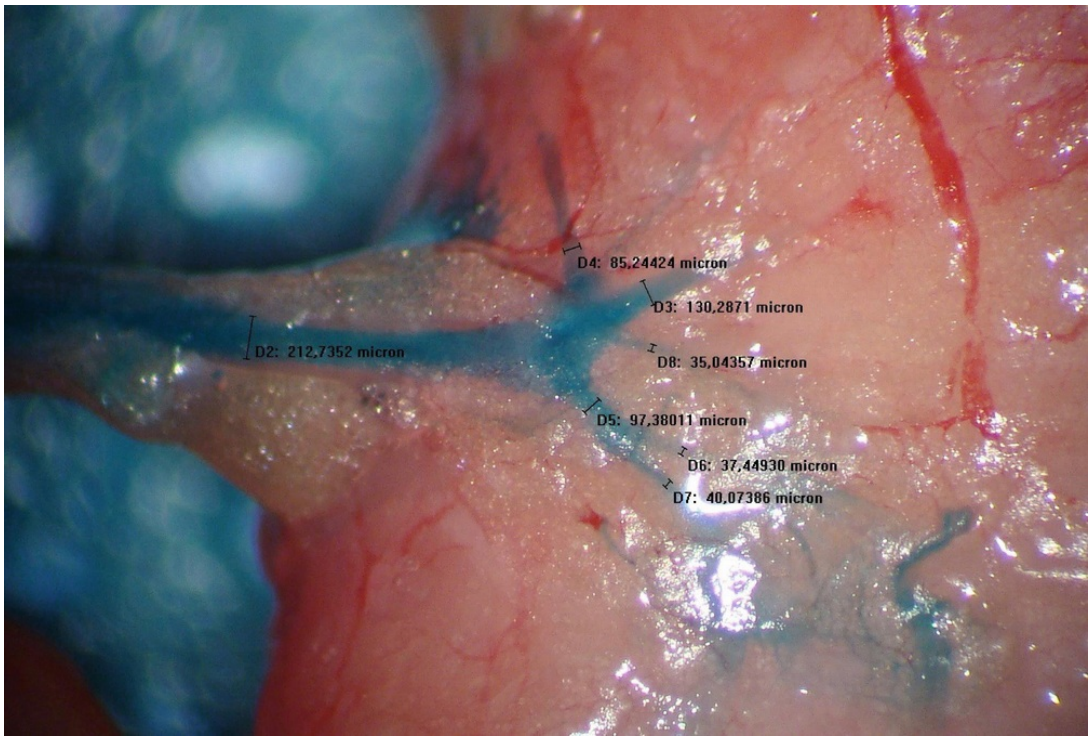

Fig. 4.39 Mophometric data of the lymphatic vessel at the level of lymphonodular transition and capsule. Lymphatic perfusion in the study area is not compromised

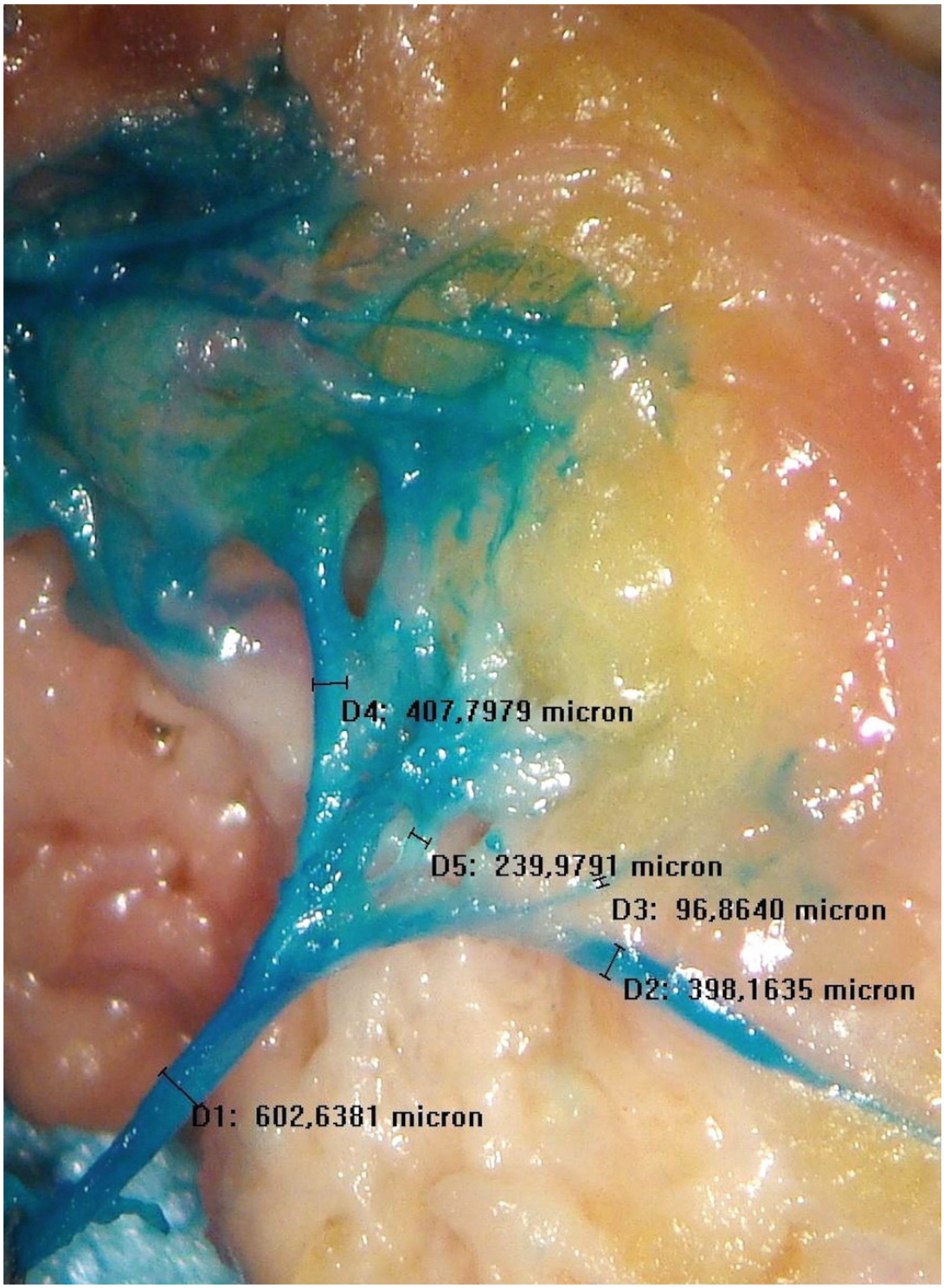

Fig. 4.40 Antegrade color lymphography of inflow lymphatic vessel of scattered type. The lymph node is affected by metastasis. The D3 vessel has the smallest diameter and a metastatic affected area

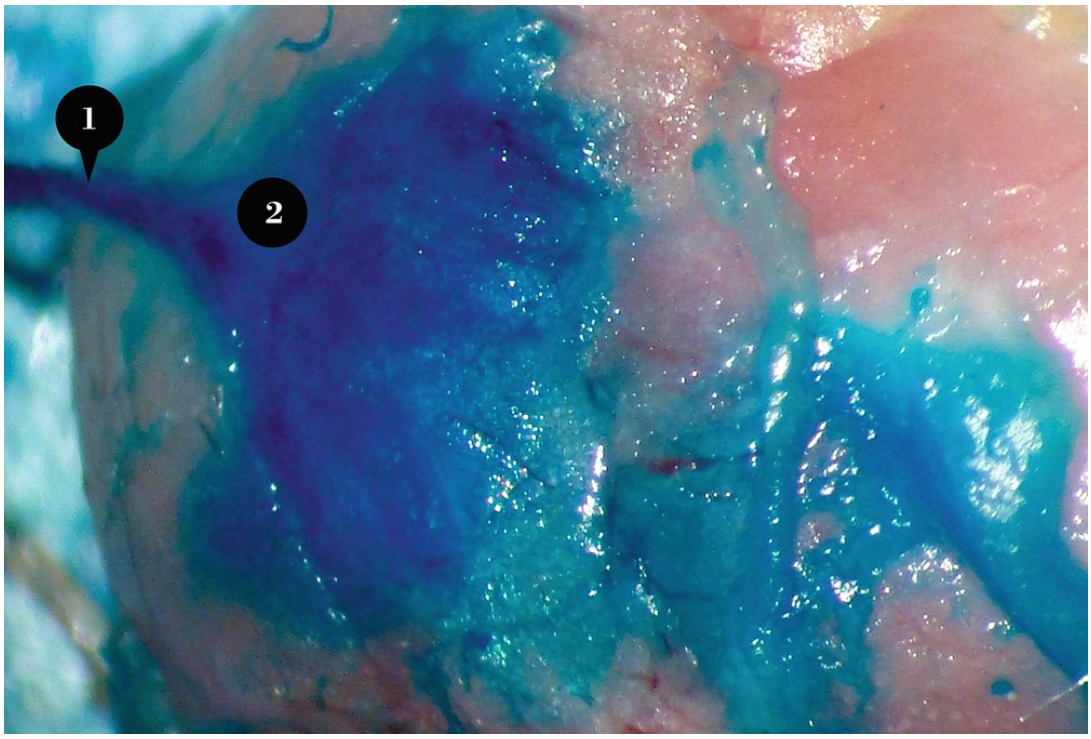

Fig. 4.41 The color contrast filled the inflow lymphatic vessel (1) and a part of the lymph node sinus (2)

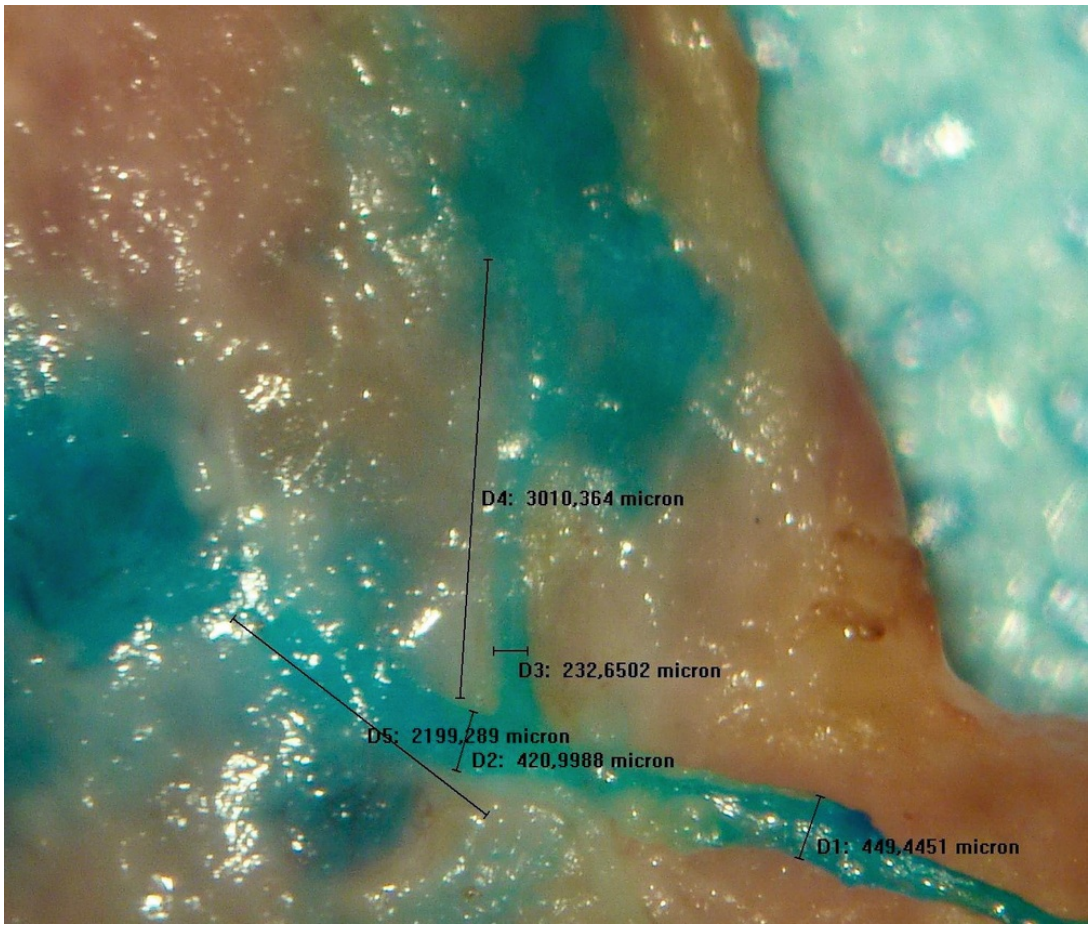

Fig. 4.42 Color lymphography of lymphonodular transitional region. The inflow vessel has a diameter of 449 μm. This vessel is divided into two branches with a total diameter of 452 μm. There are no signs of metastatic block of the lymph node lobe

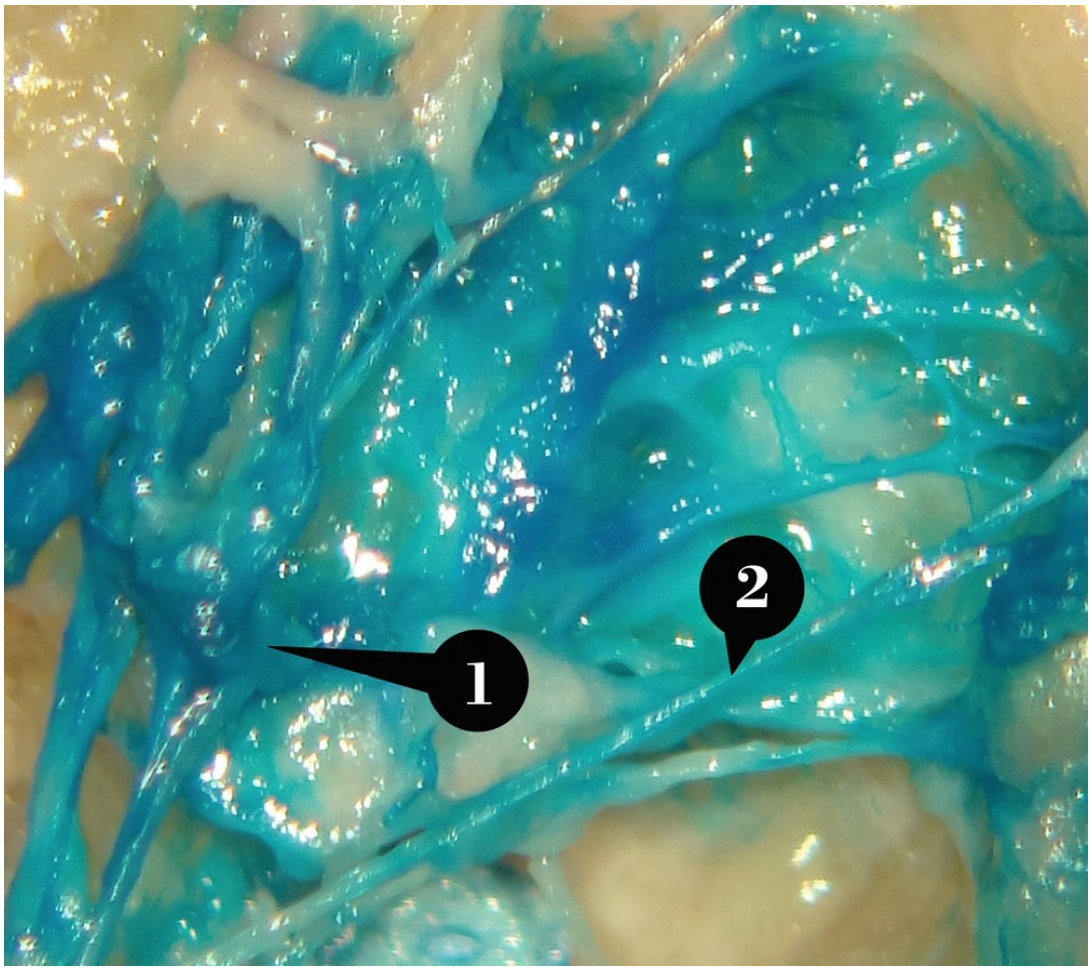

Fig. 4.43 A wide and developed vascular bed of axillary fat in breast cancer. The vessels have different diameters, tortuous and saccular dilatation, and glomeruli (1). Figure 2 illustrates the great vessel. By contrast to this, there was used the method of chromolymphography

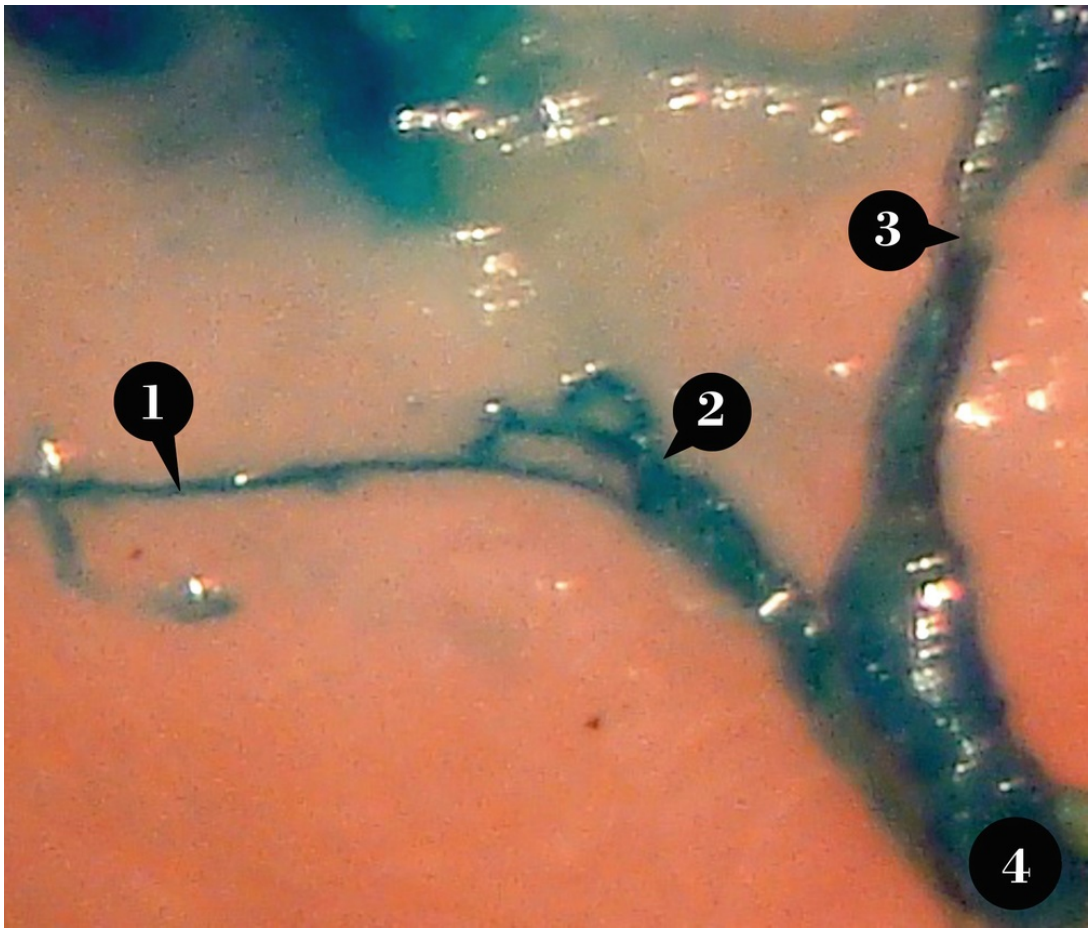

Fig. 4.44 Direct color lymphography of vessels penetrating the lymph node. Figure 3 illustrates the great lymphatic vessel, the left branch of the vessel (1,2) is sharply constricted (1), and the main trunk is blocked (2). The right branch also has a sharp constriction (4)

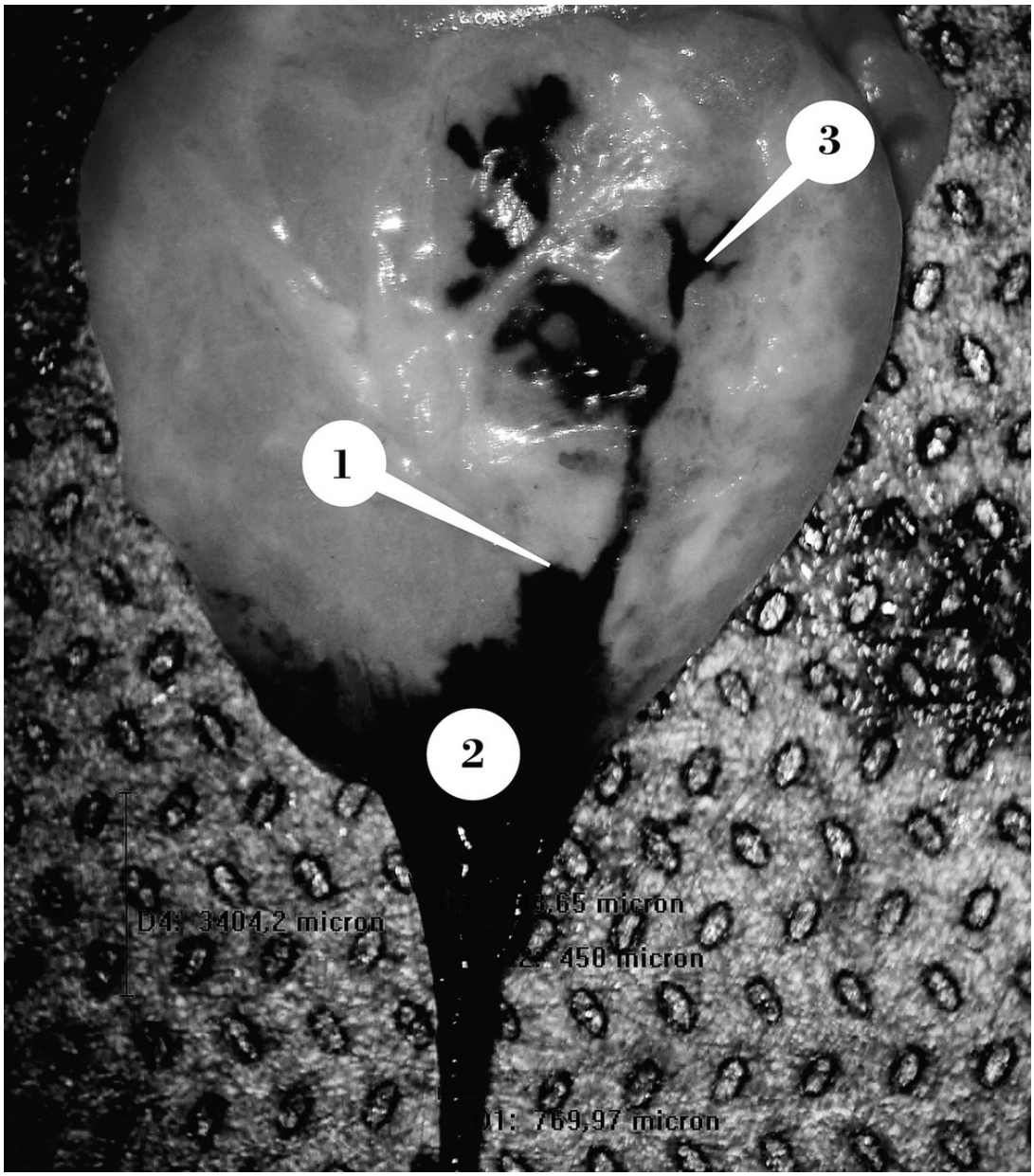

Fig. 4.45 The black and white film demonstrating chromolymphography of inflow vessel and vessels located in the lymph node capsule. Figure 2 illustrates the area of lymphonodular transition filled with contrast medium and 1 symptom of amputation of one of the lymphatic vessel branches. This symptom is characteristic for metastatic blocking of a lymphatic vessel. 3 illustrates zone of free perfusion

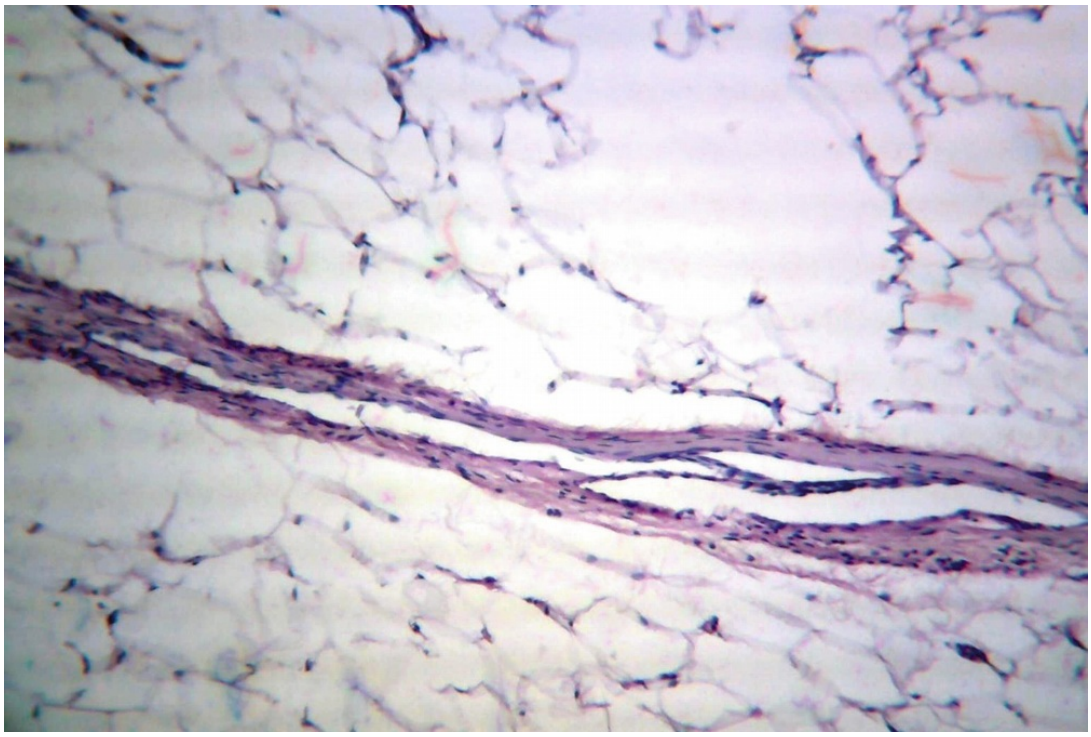

Fig. 4.46 Lymphatic vessel located in adipose tissue of the axillary region. There are cusps in the lumen of the vessel. Hematoxylin and eosin stain

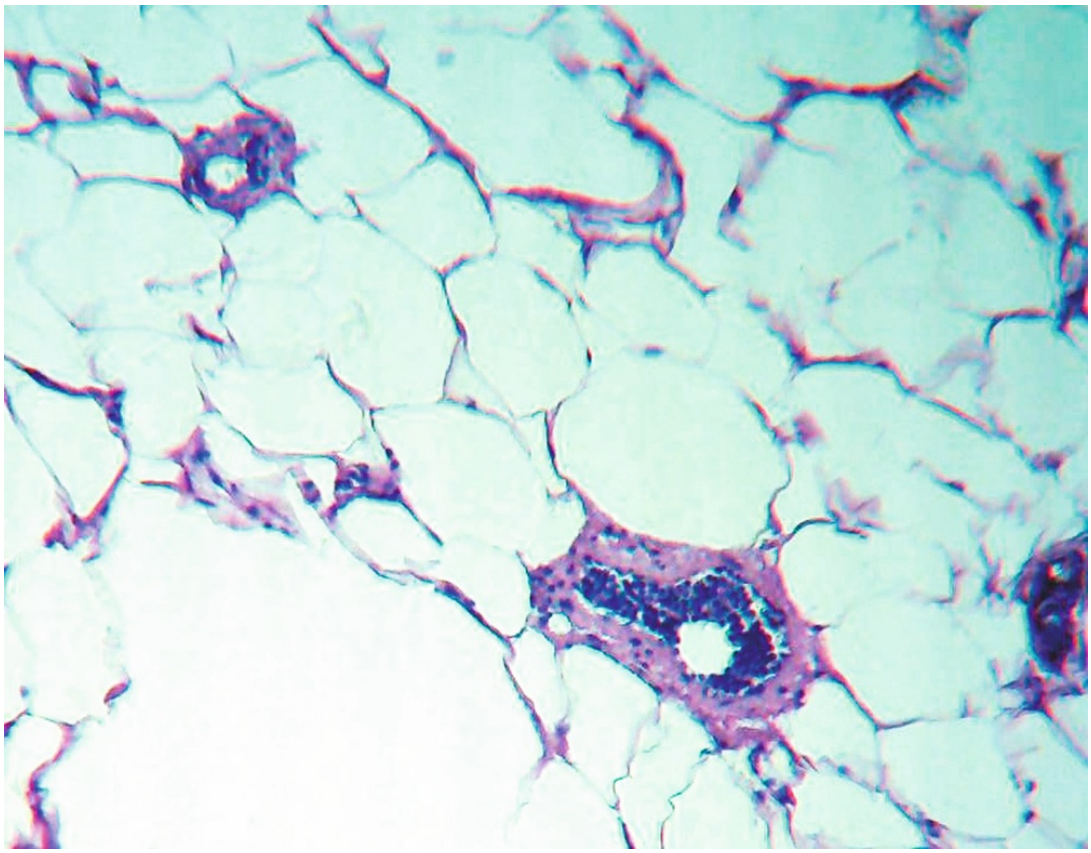

Fig. 4.47 Adipose involution of the lymph node. Lymphocyte aggregates in intranodal vessels. Hematoxylin and eosin stain

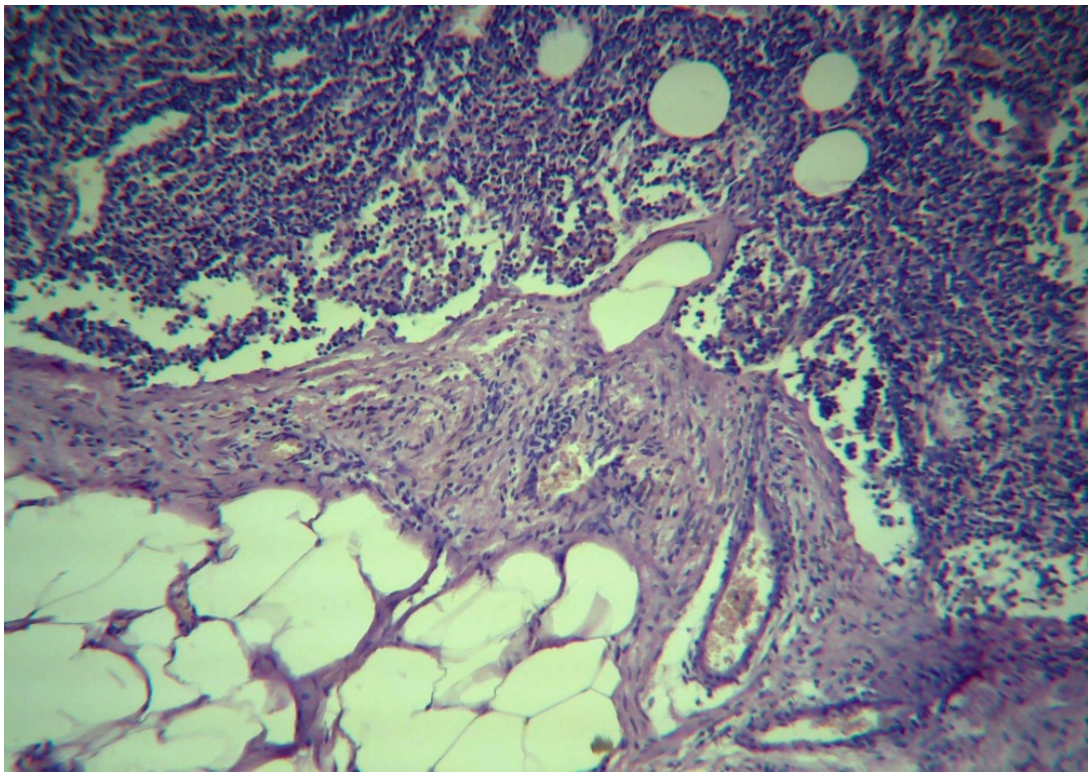

Fig. 4.48 Neo-lymphangiogenesis of the lymph node capsule in breast cancer. Hematoxylin and eosin stain

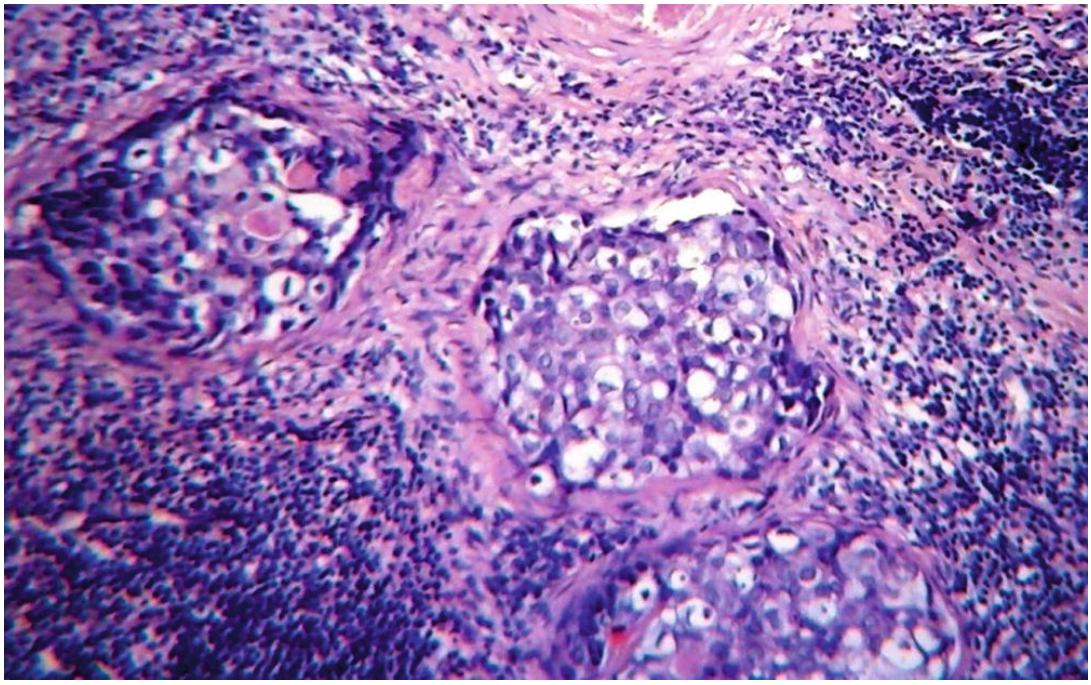

Fig. 4.49 Metastatic embolus in the vessel of the lymph node capsule. The vessel perfusion is partially preserved. Hematoxylin and eosin stain

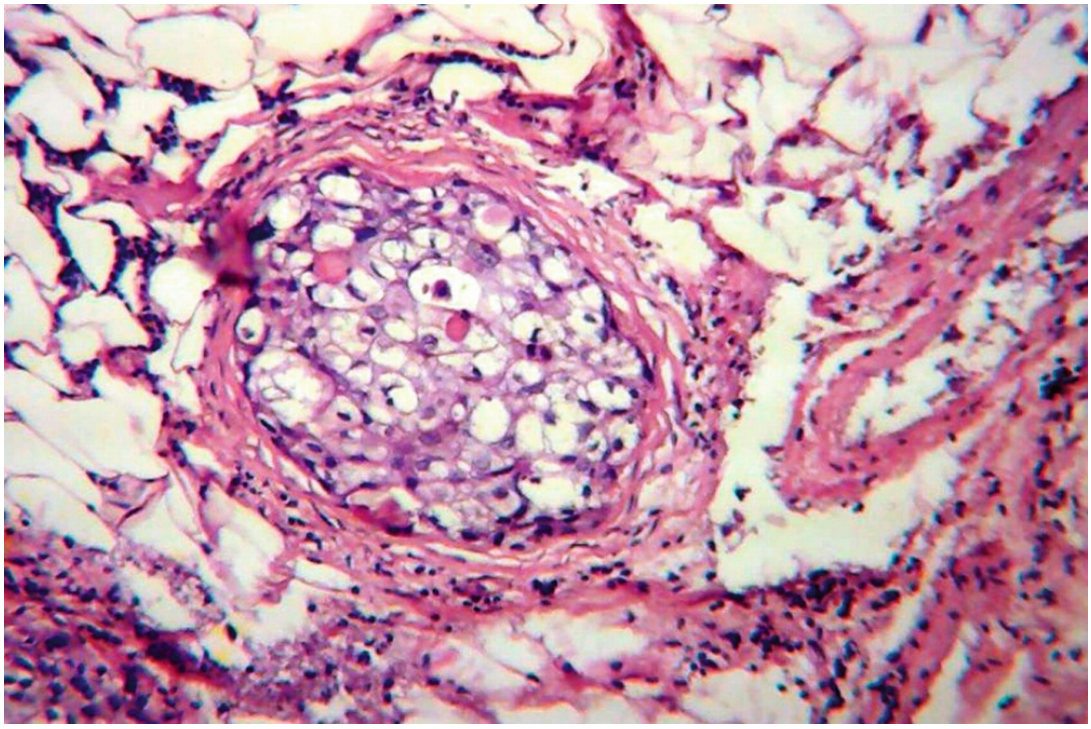

Fig. 4.50 Metastatic cascade: occlusion of afferent lymphatic vessels in breast cancer. The diameters of vessels reach 281, 216, and 150 μm. Hematoxylin and eosin stain

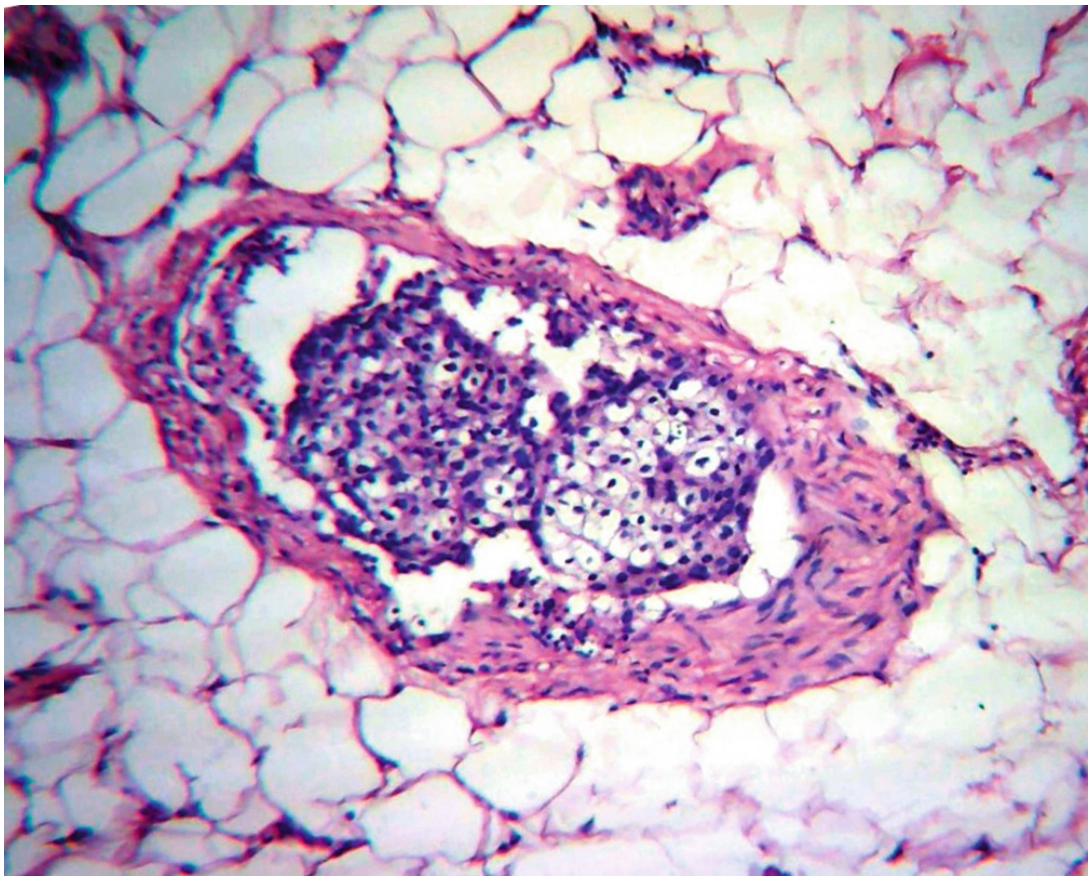

Fig. 4.51 Conglomerations of cancer cells in inflow lymphatic vessels. The diameter of a large vessel reaches 305 μm. Hematoxylin and eosin stain

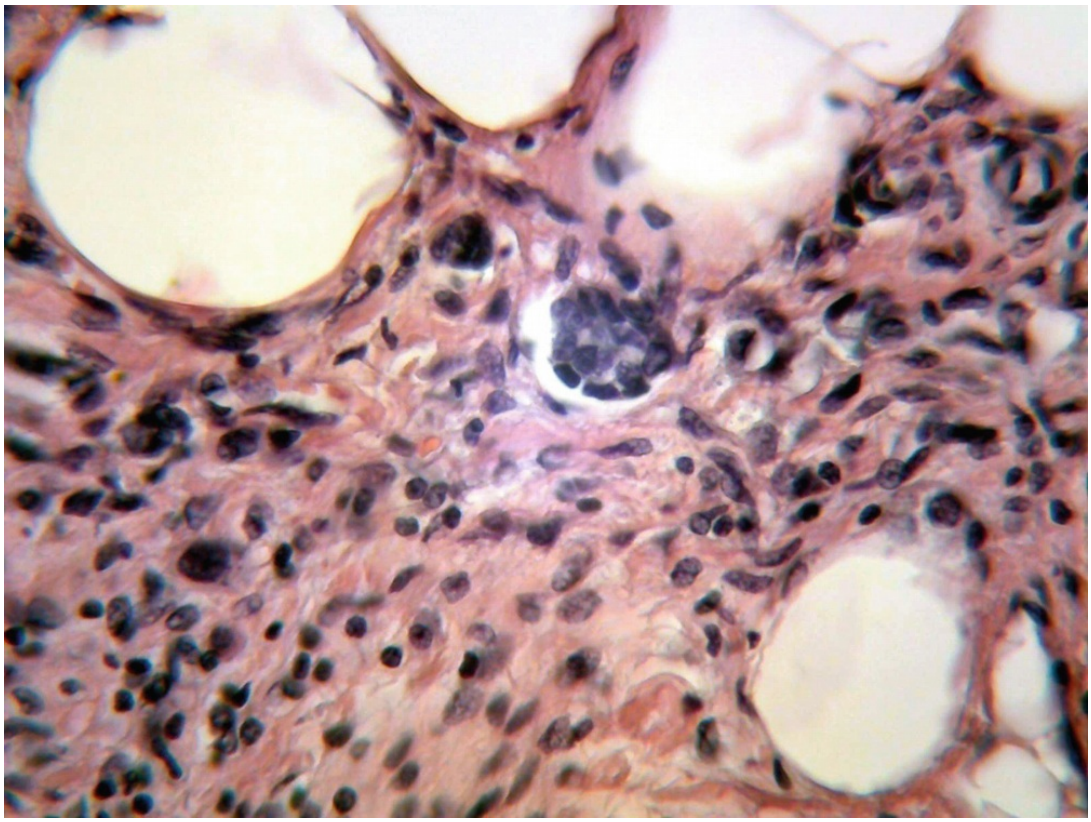

Fig. 4.52 Tumor emboli in lymphatic vessel. Hematoxylin and eosin stain

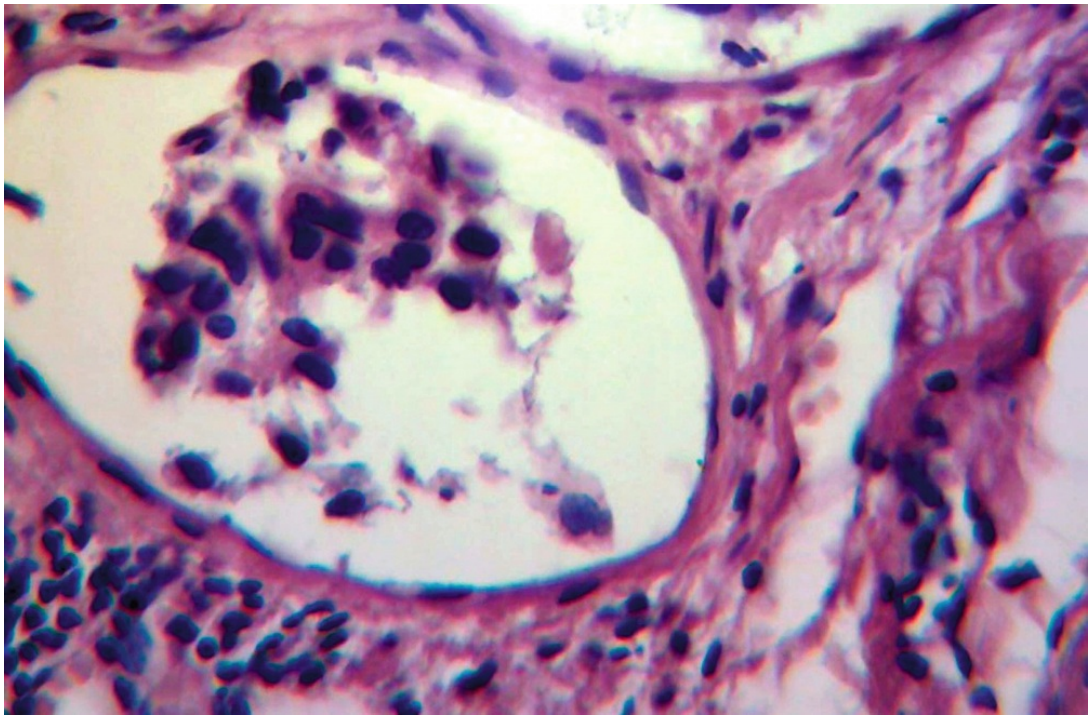

Fig. 4.53 Vessels of the lymph node capsule are partially blocked by tumor

metastatic conglomerations. Hematoxylin and eosin stain

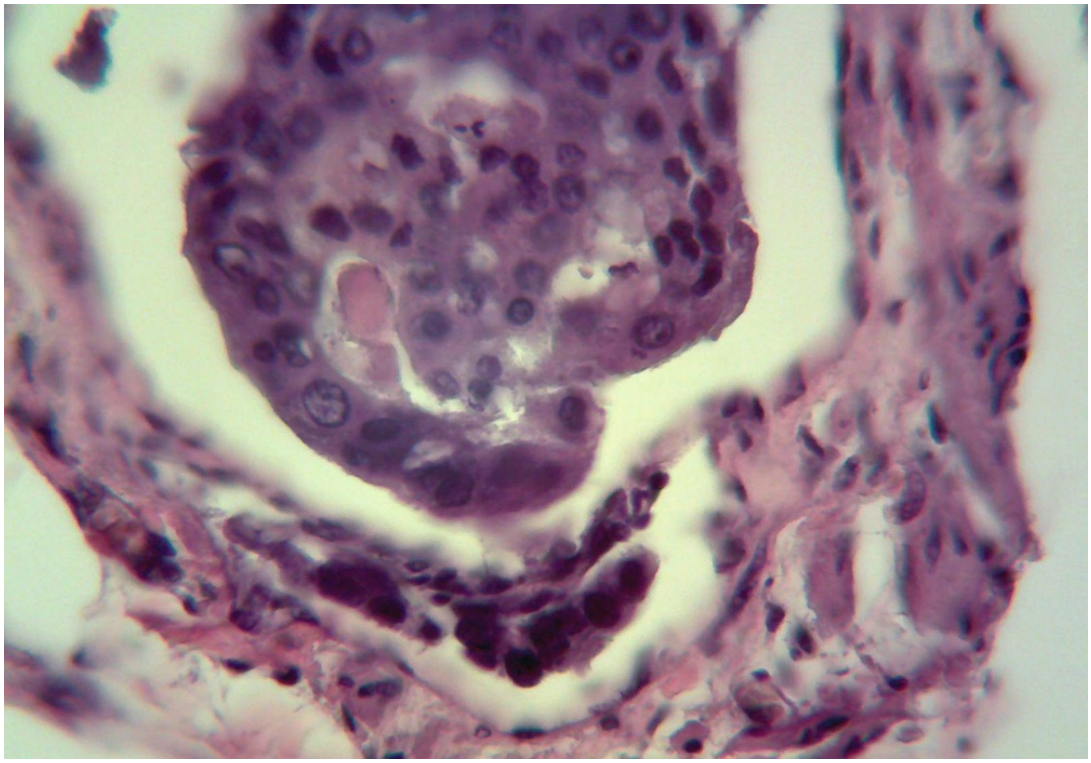

Fig. 4.54 Lymphatic vessel filled with a conglomerate of tumor cells, making lymphokinesis difficult. Hematoxylin and eosin stain

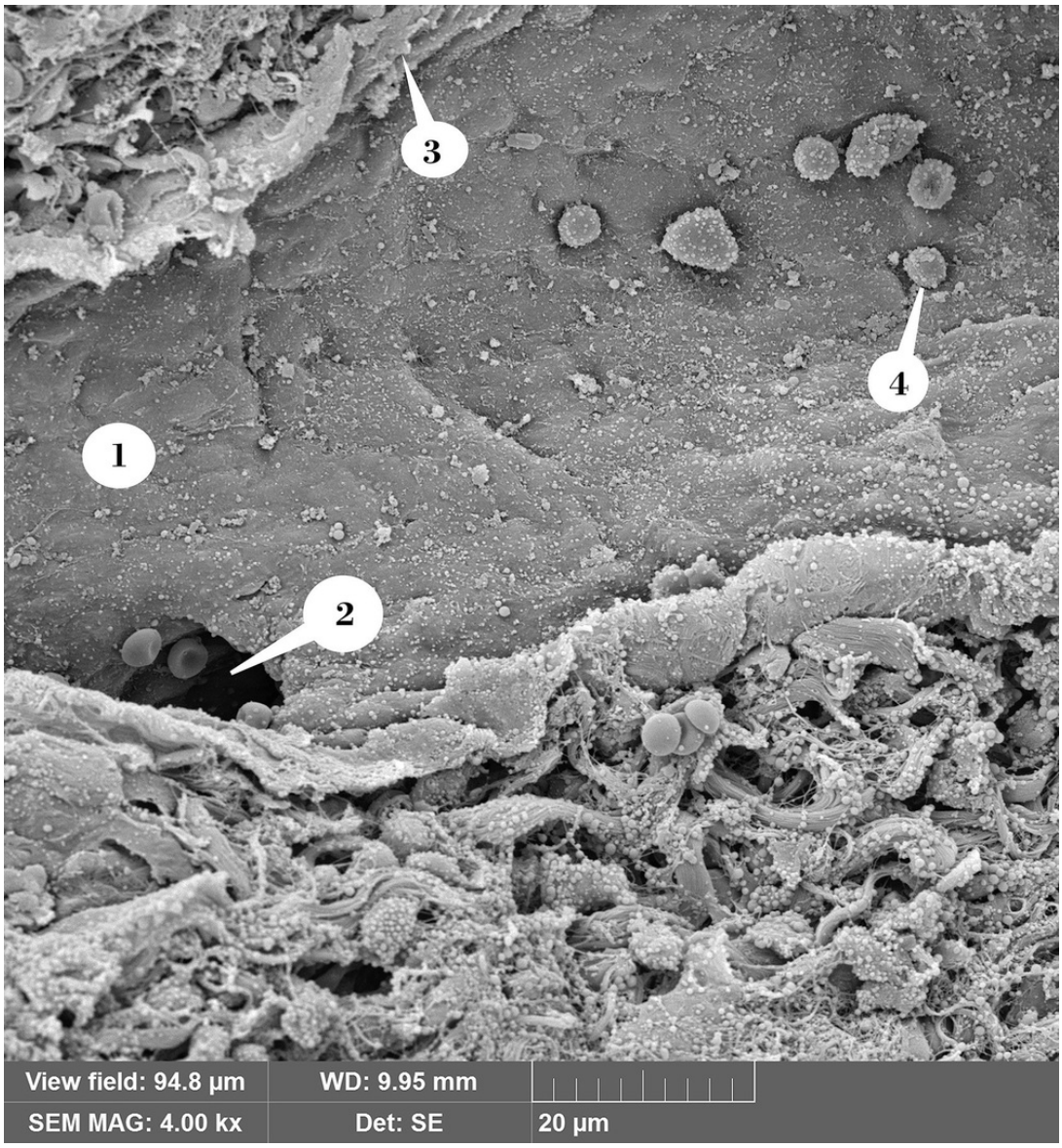

Fig. 4.55 Luminal lymphatic vessel (1) in electron microscopy. The figure illustrates a luminal intervascular anastomosis (2), endothelial tissue (3), and a few lymphocytes (4). Lymphocyte aggregates are visible outside the vascular bed

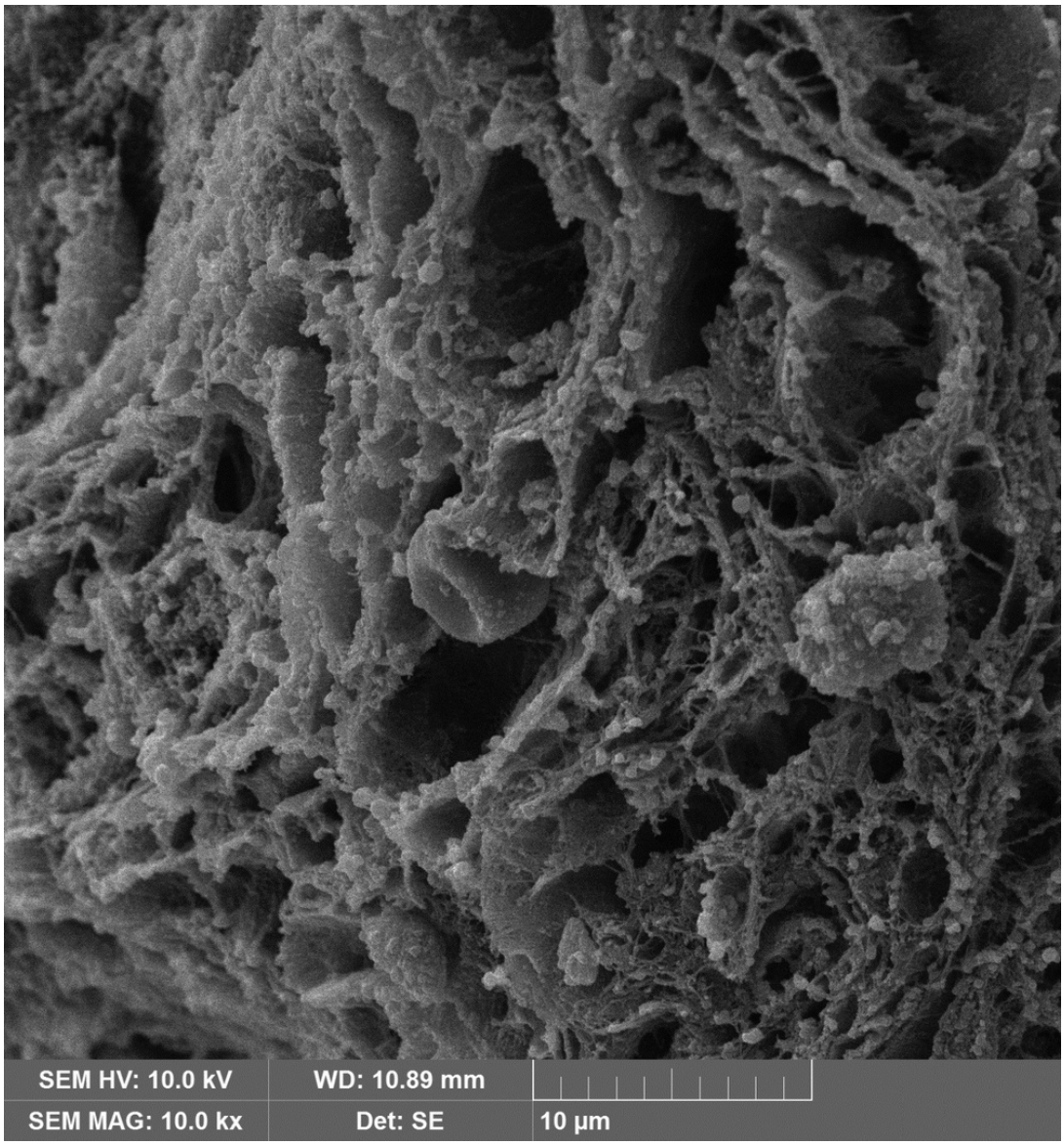

Fig. 4.56 Electron microscopy. Sinus of the lymph node; there are luminal sinus lymphatic capillaries and many lymphocytes. Tumor cells are visible; the surface is covered by lymphocytes

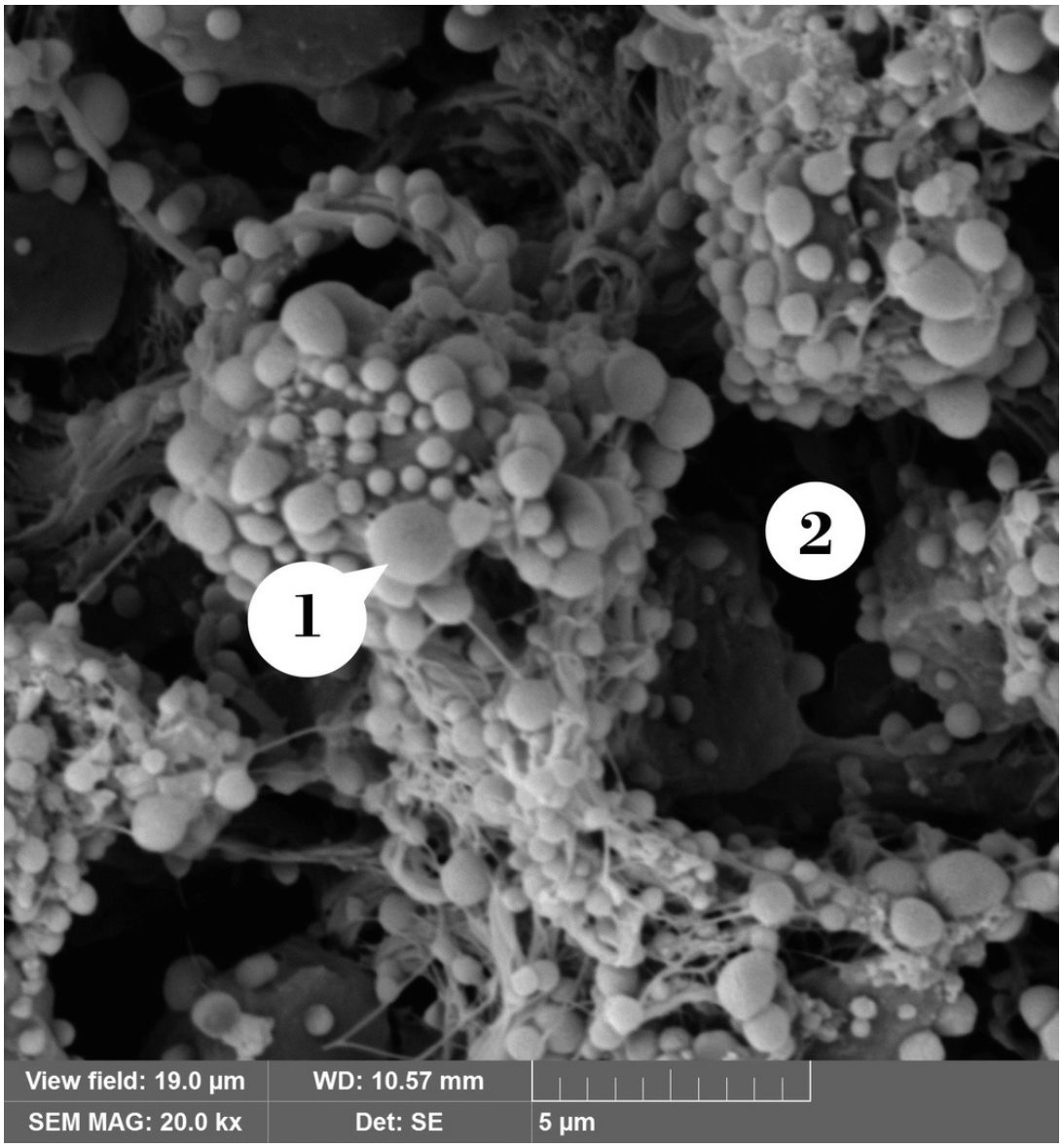

Fig. 4.57 Electron microscopy. The luminal lymphocyte aggregates (in the sinus). Lymphocytes cover the surface of cancer cell (1) forming conglomeration. 2 – free space of sinus. There are six cancer cells

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5. Neolymphogenesis

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Keywords Lymphatic system – Axillary lymphatic apparatus – Breast cancer – Neolymphogenesis – Organogenesis – Tertiary lymphoid organs

The term “neolymphogenesis” is still at the stage of thinking, and not all scientists and representatives of practical medicine agree with this concept, much less with this fact. But there is nothing wrong with this. History remembers an enormous number of discoveries that were denied and not admitted by society as a reality. However, the years passed and the “fiction” described a few decades ago was recognized as a reality. The same thing goes for this term and the essence of this phenomenon. The term “neolymphogenesis” is a working version. It can always be edited. There are scientific descriptions of tertiary lymphatic formations in some human diseases. However, exactly our research team

established the fact of prosthesis of the lymphatic apparatus in cancer and precisely at that moment when the sentinel lymph node function is completely exhausted. In our studies, we did not find these changes during the early stages of cancer and even in the first lymph node metastases. This phenomenon starts at a certain point: it has yet to be established and proved. Nevertheless, we declare a real postnatal neolymphogenesis in cancer and we have an evidence base for this.

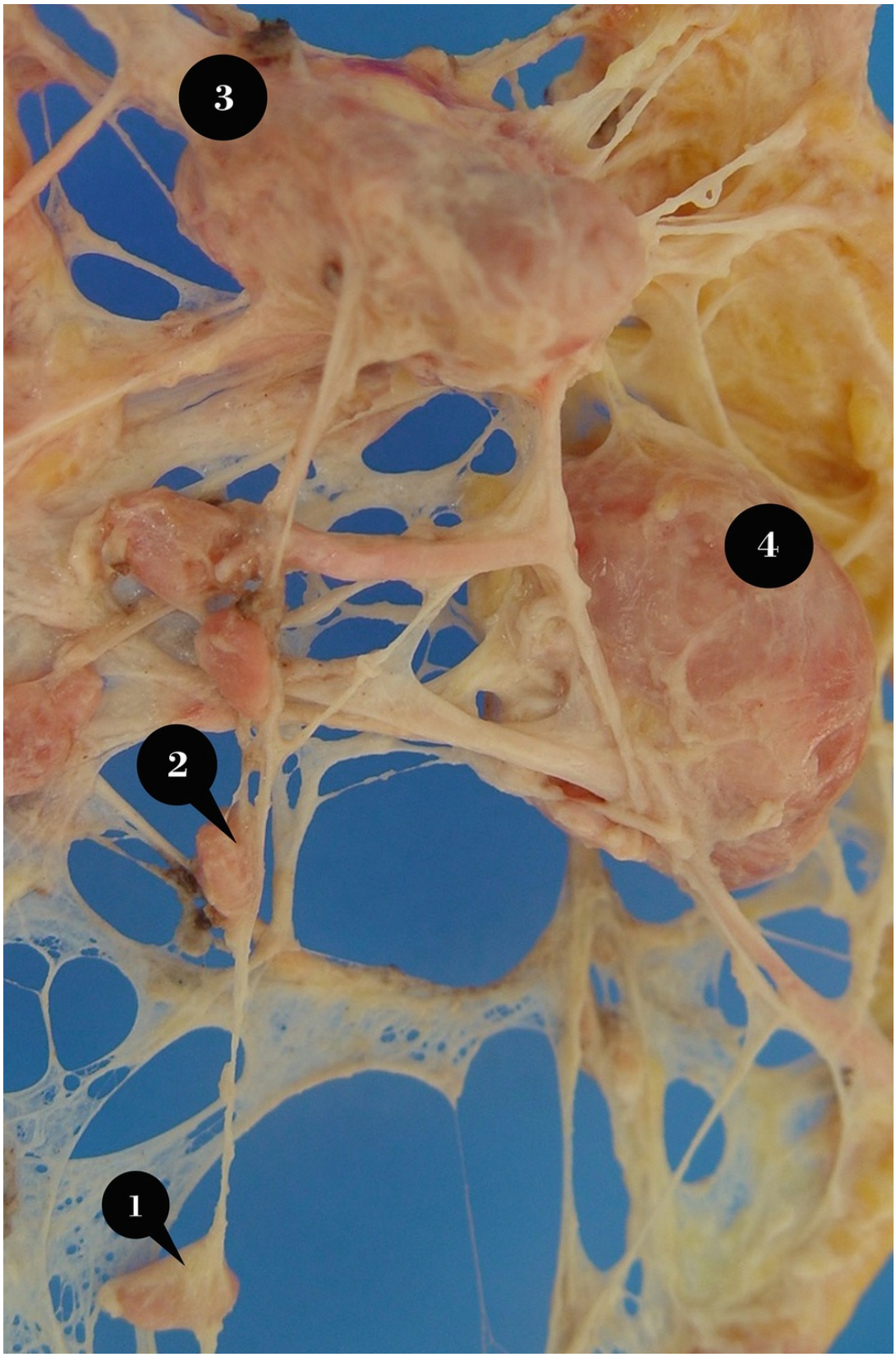


Fig. 5.1 The fragment of lymphatic mapping in breast cancer. Figures 3 and

4 illustrate the lymph nodes, circular and elliptically shaped, up to 30 mm in diameter, the capsule with scarring. The 3 lymph node (sentinel) is connected to a vessel with tertiary lymphatic formations (1, 2) (newly formed lymph nodes). These nodes are in series 1 after another and are connected by one vessel. At first this vessel is inflow one, but after it outflows from the node, it becomes an efferent one

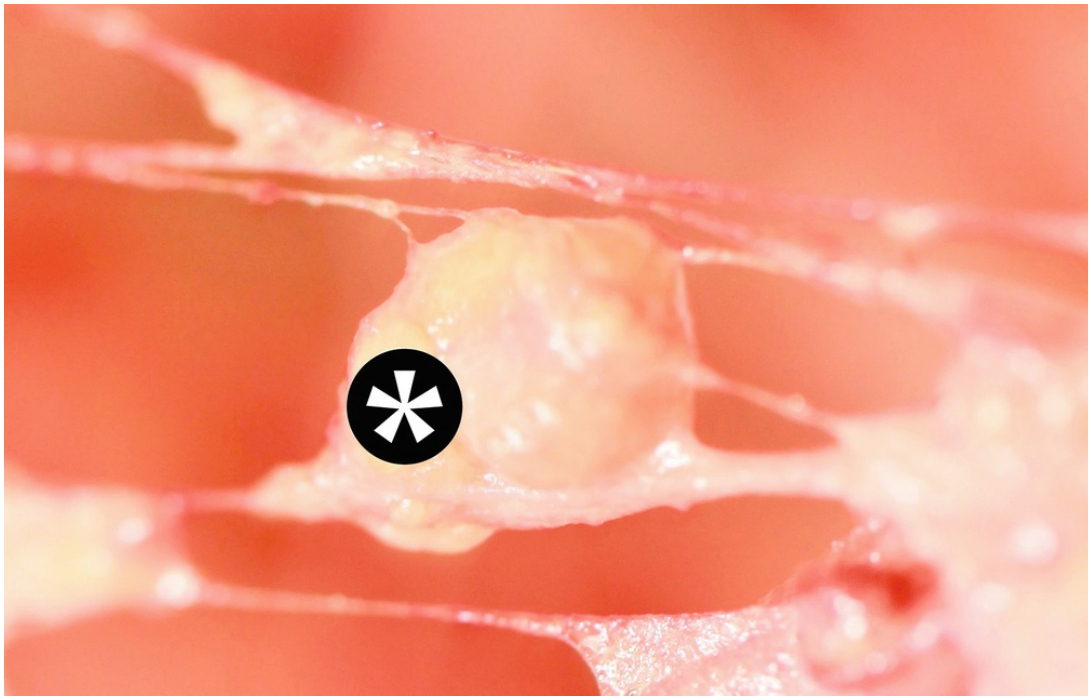


Fig. 5.2 The same lymph node (∗) in another projection. A large lymphatic vessel on which the node is located is visible. The node capsule contains an adipose tissue

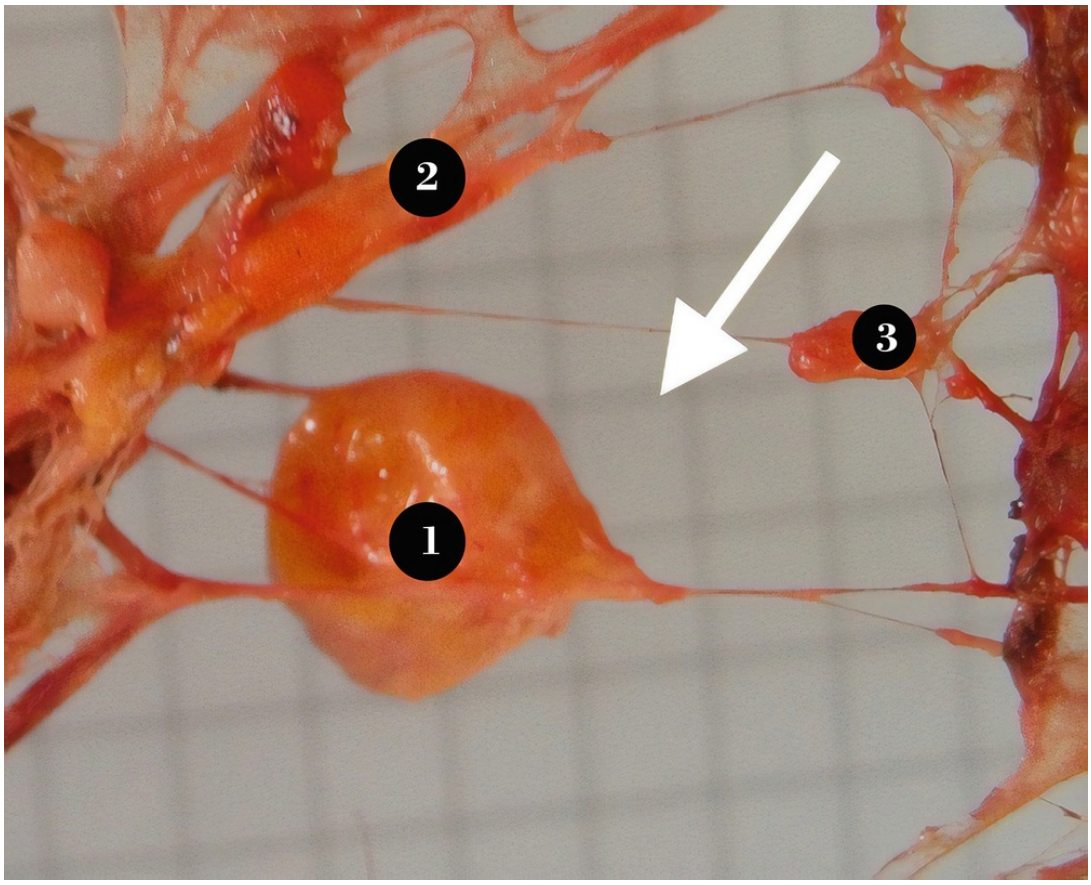


Fig. 5.3 The fragment of lymphatic mapping of the axillary region in breast cancer. Figure 1 illustrates postnatal lymph node, 2 the great lymphatic vessels, and 3 adherence of several lymphatic vessels. The lymph node is well- formed, surrounded by several newly formed vessels of small diameter. In the field of lymphatic vessel adherence, there is a formation which is the stage of neolymphogenesis

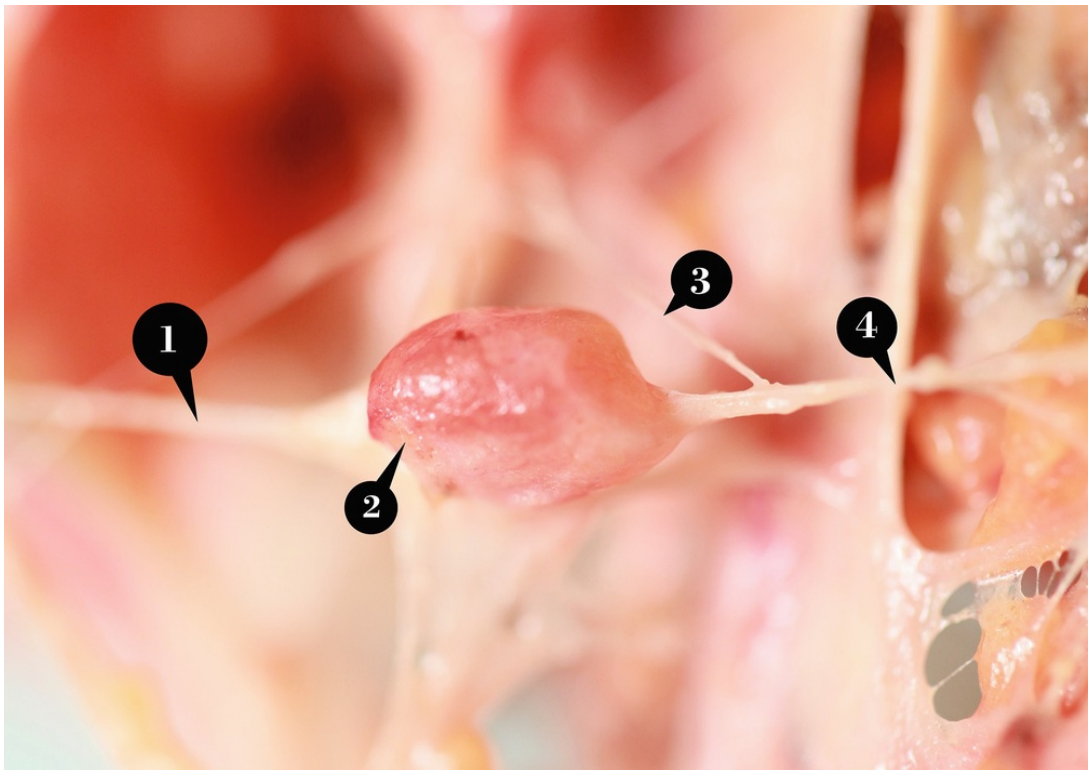


Fig. 5.4 A single lymph node 2 having a primary connection with the great vessel 1 and 4. This vessel is interconnected with other nodes and vessels through the collateral capillaries 3. The base of the lymph node capsule is extremely pale; its surface is inhomogeneous

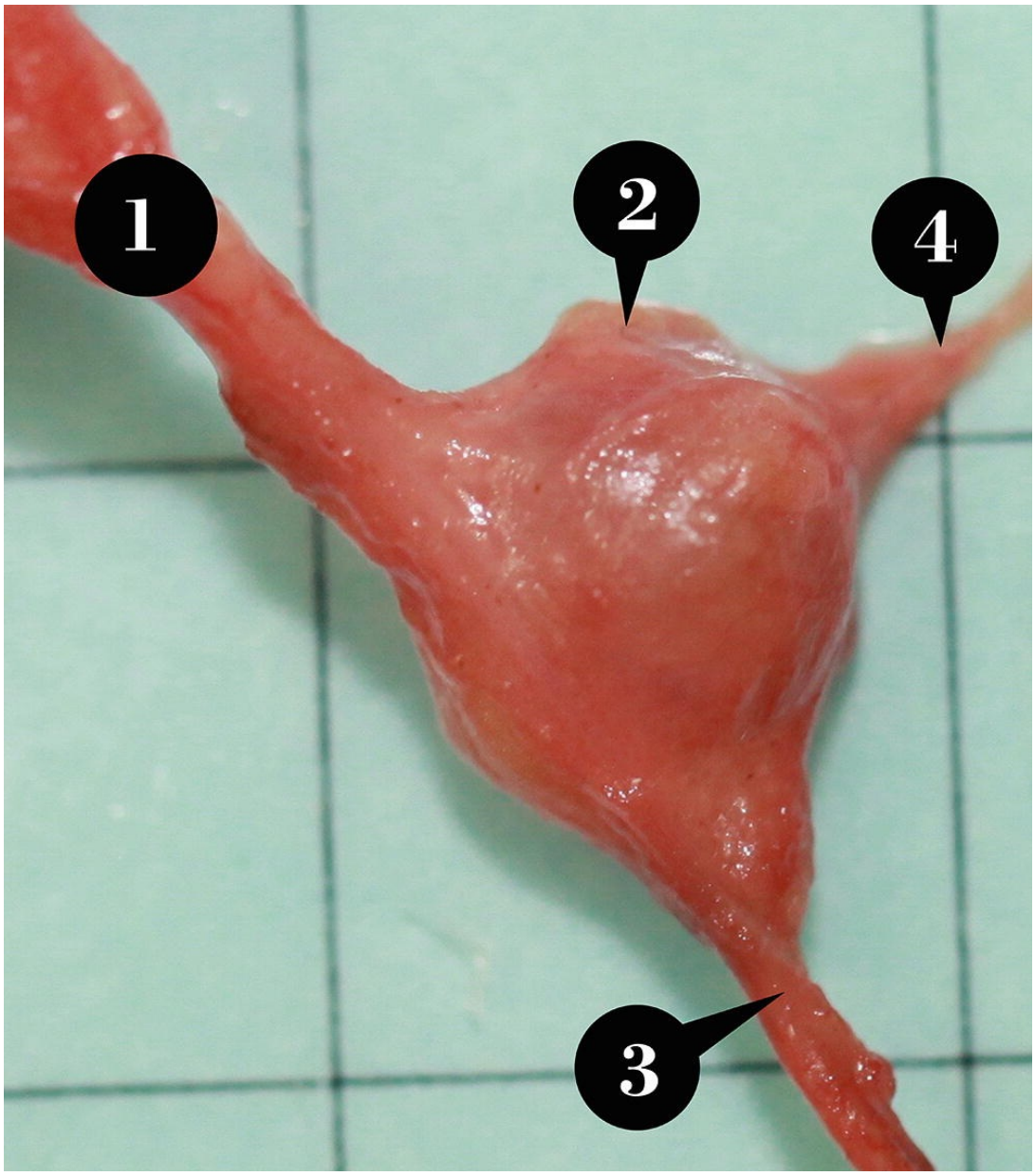


Fig. 5.5 The lymph node (2) is located on a well-formed great vessel (1 and 3) which performs the function of the lymph flow and outflow. The node is spherical; the capsule is tense. Another lymphatic vessel enters the node (4)

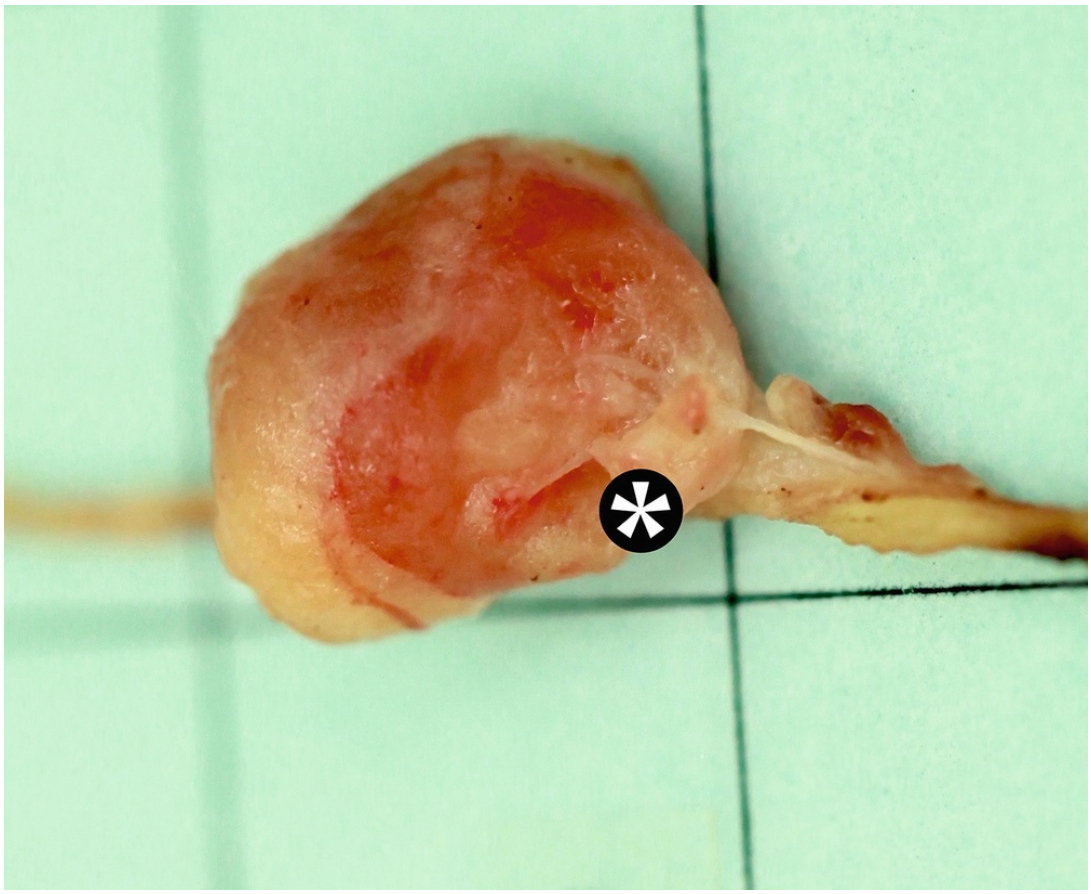


Fig. 5.6 A single lymph node isolated from the complex (∗); it has an atypical anatomical organization. Its size reaches 10 mm; it has one inflow and efferent vessel. The lymph node itself is well-formed and has a massive capsule

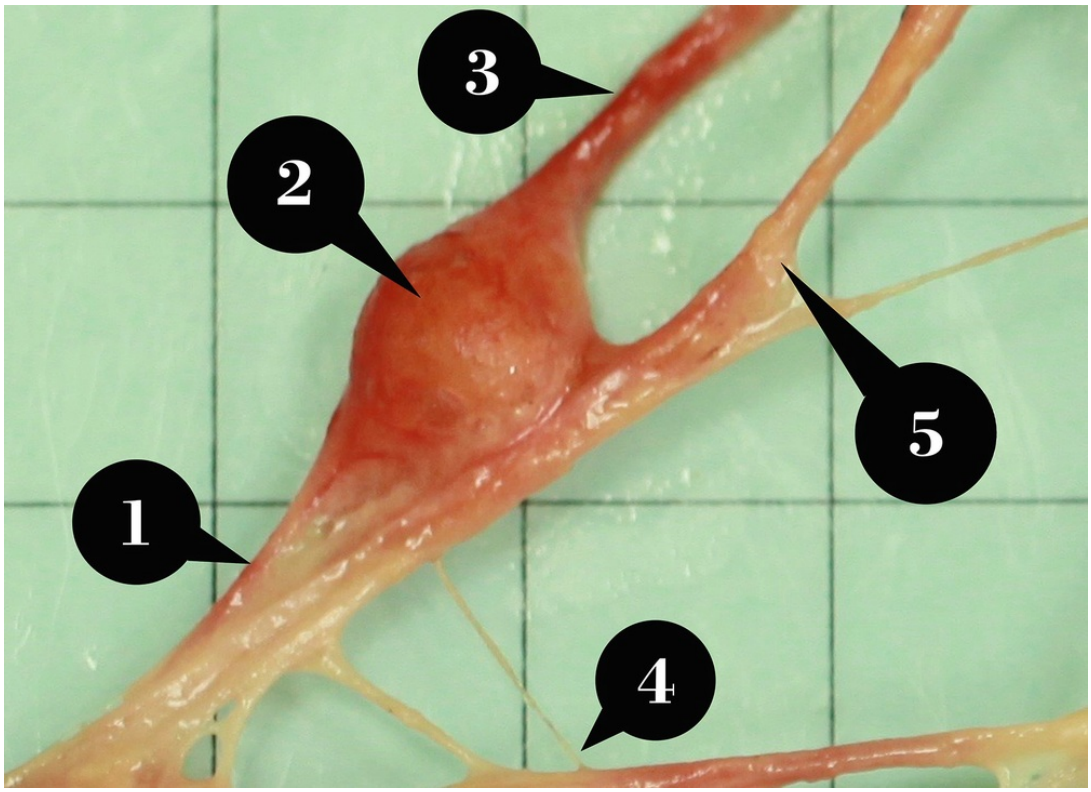


Fig. 5.7 Targeted lymph node dissection (2). Figures 1 and 3 illustrate a lymphatic vessel that is connected to a node. 5 illustrates the great vessel which bypasses the node, but closely adjacent to its capsule. The great vessels are joined together by newly formed lymphatic vessels (4)

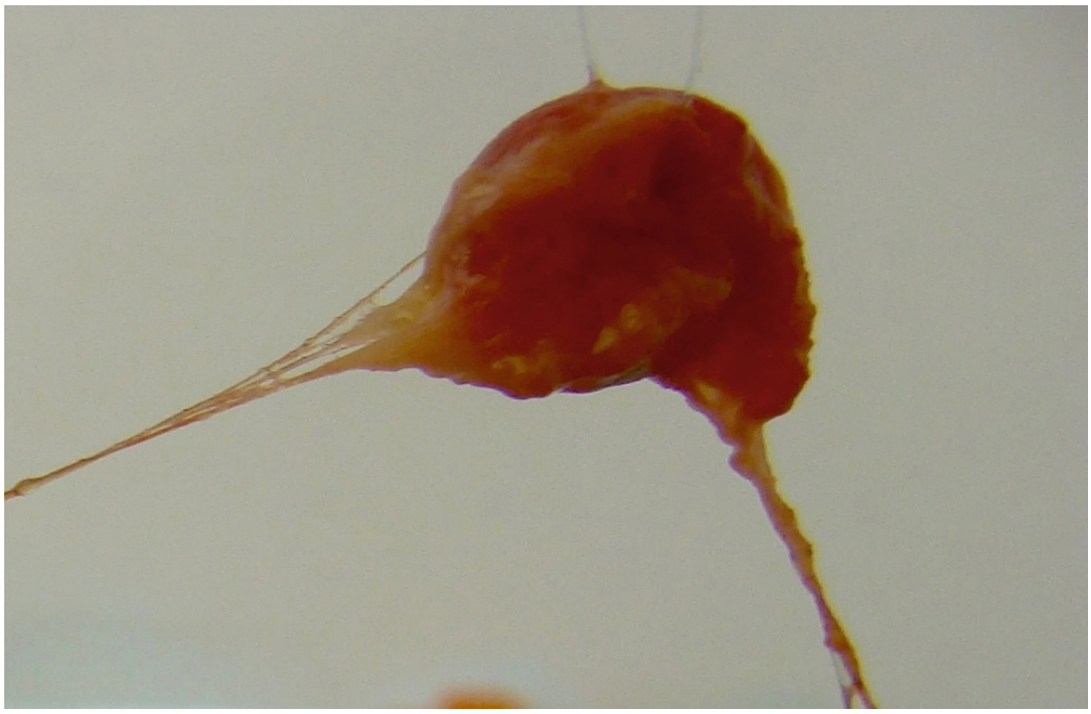


Fig. 5.8 A single lymph node formed on a single lymphatic vessel (inflow and efferent ones). The node drainage is provided by newly formed lymphatic vessels

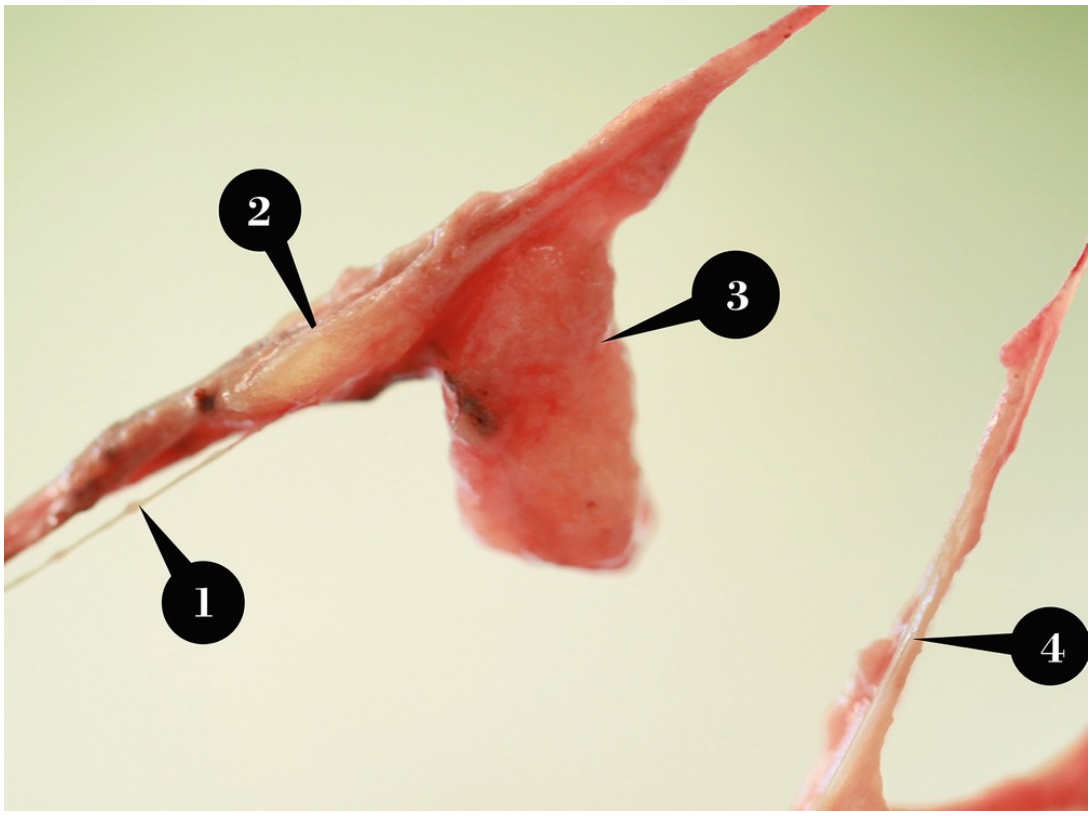


Fig. 5.9 Atypical (postnatal) lymph node (3) which is located on the great lymphatic vessel (2). Figure 1 illustrates a newly formed lymphatic vessel and 4 adjacent great lymphatic vessel. The lymph node (3) is about 10 mm; the capsule is pale and inhomogeneous

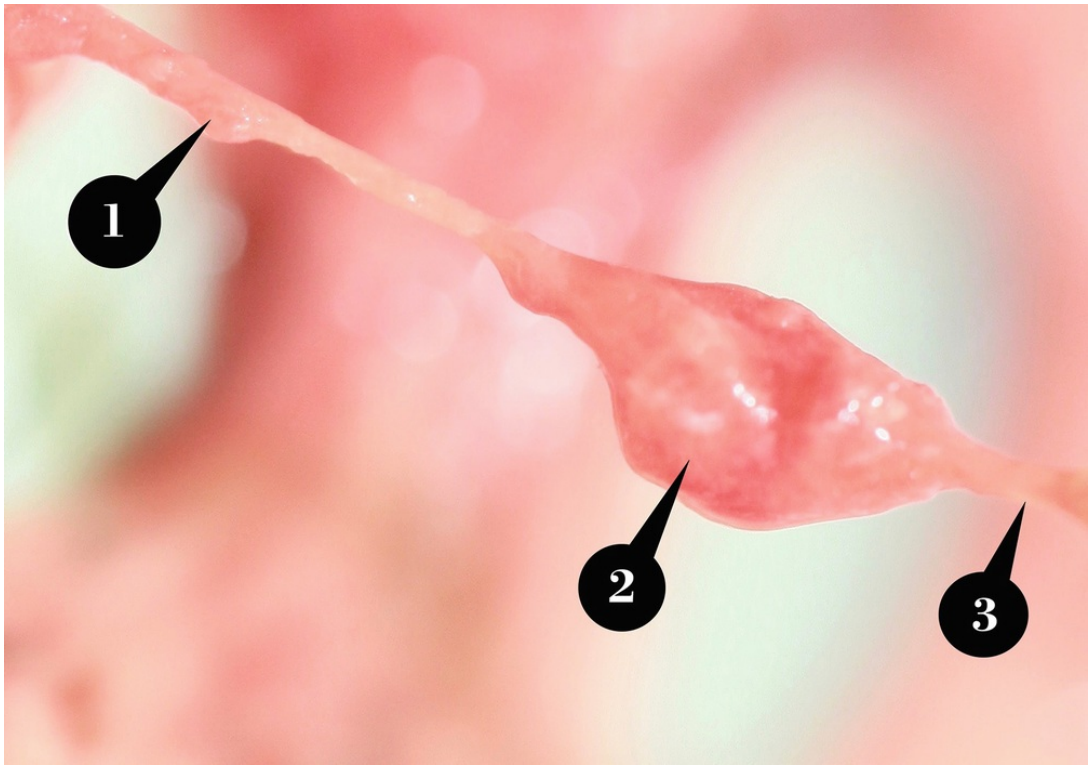


Fig. 5.10 A single lymph node (2) located on one great vessel (3). There is a swelling (plus tissue) of the lymphatic vessel (1) which can be a source of the tertiary lymphoid organ. The lymph node capsule 2 is inhomogeneous; the node has many nodal structures

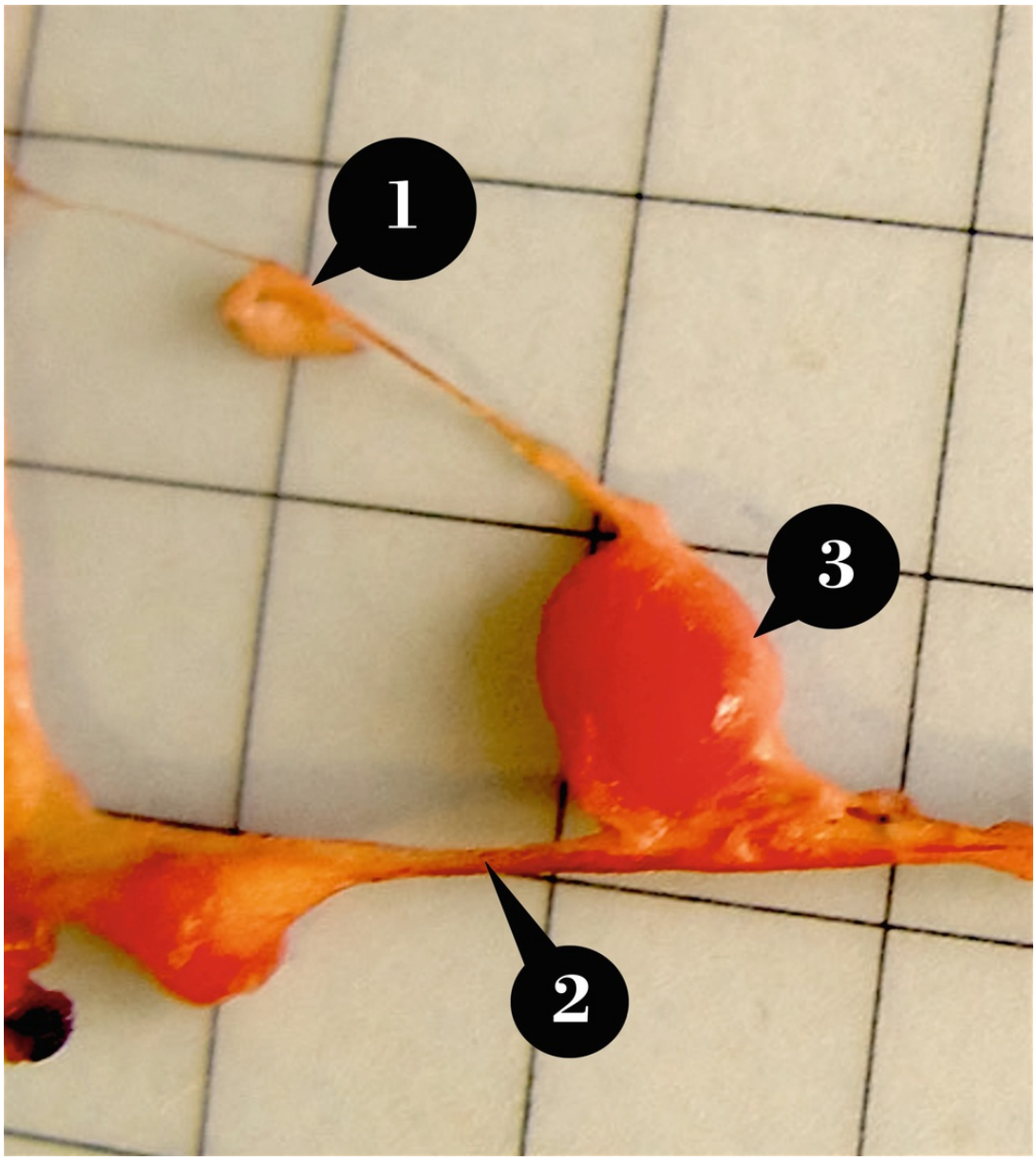


Fig. 5.11 A single lymph node (2) located on one great vessel (3). There is a swelling (plus tissue) of the lymphatic vessel (1) which can be a source of the tertiary lymphoid organ. The lymph node capsule 2 is inhomogeneous; the node has many nodal structures

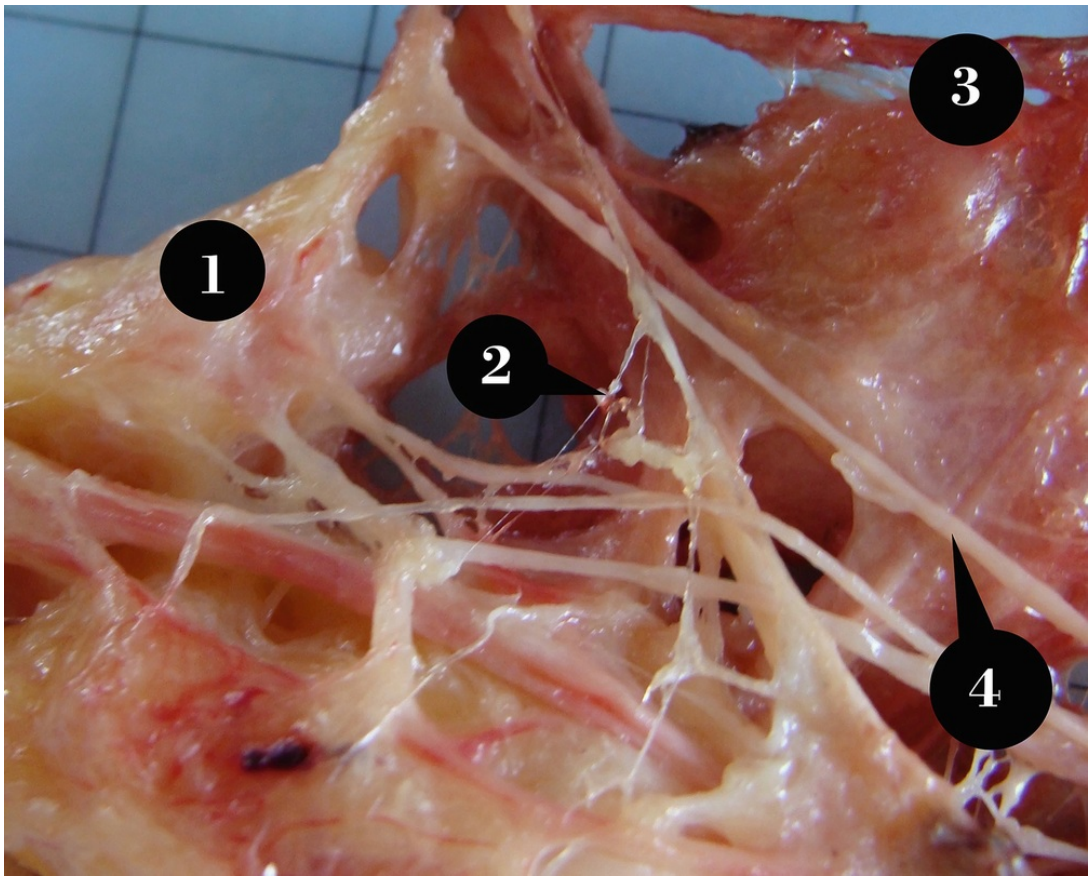


Fig. 5.12 A portion of mobilized tissues of the axillary region. Figures 1 and 3 illustrate lymph nodes affected by metastases and active neolymphogenesis, and 2 illustrates thickening of newly formed lymph nodes (stage of tertiary organs' formation) and 4 the great lymphatic vessel. The lymph node 3 is of large size, transformed into adjacent anatomical structures with infiltration of the vessel and soft tissues

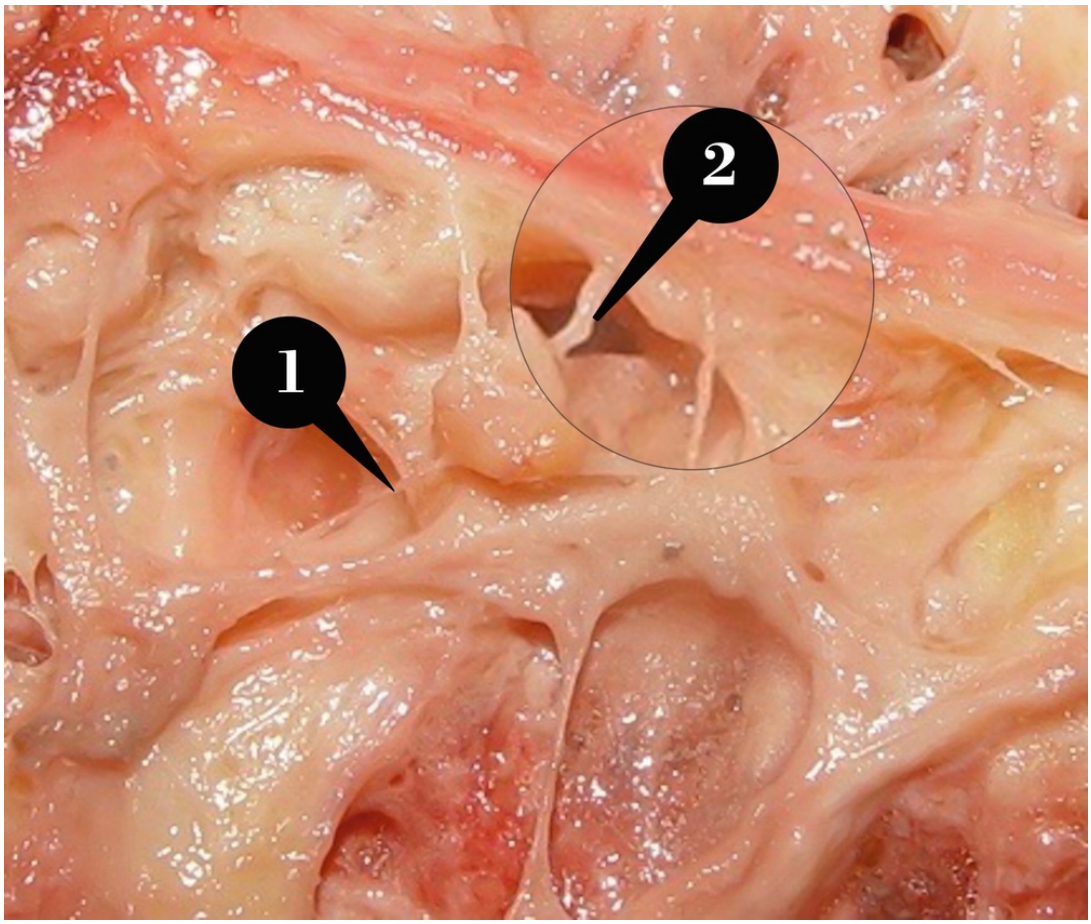


Fig. 5.13 The newly formed lymph node is surrounded by a massive stroma. Figures 1 and 2 illustrate the newly formed vessels, the node capsule is within normal limits, and it does not differ from the surrounding tissues

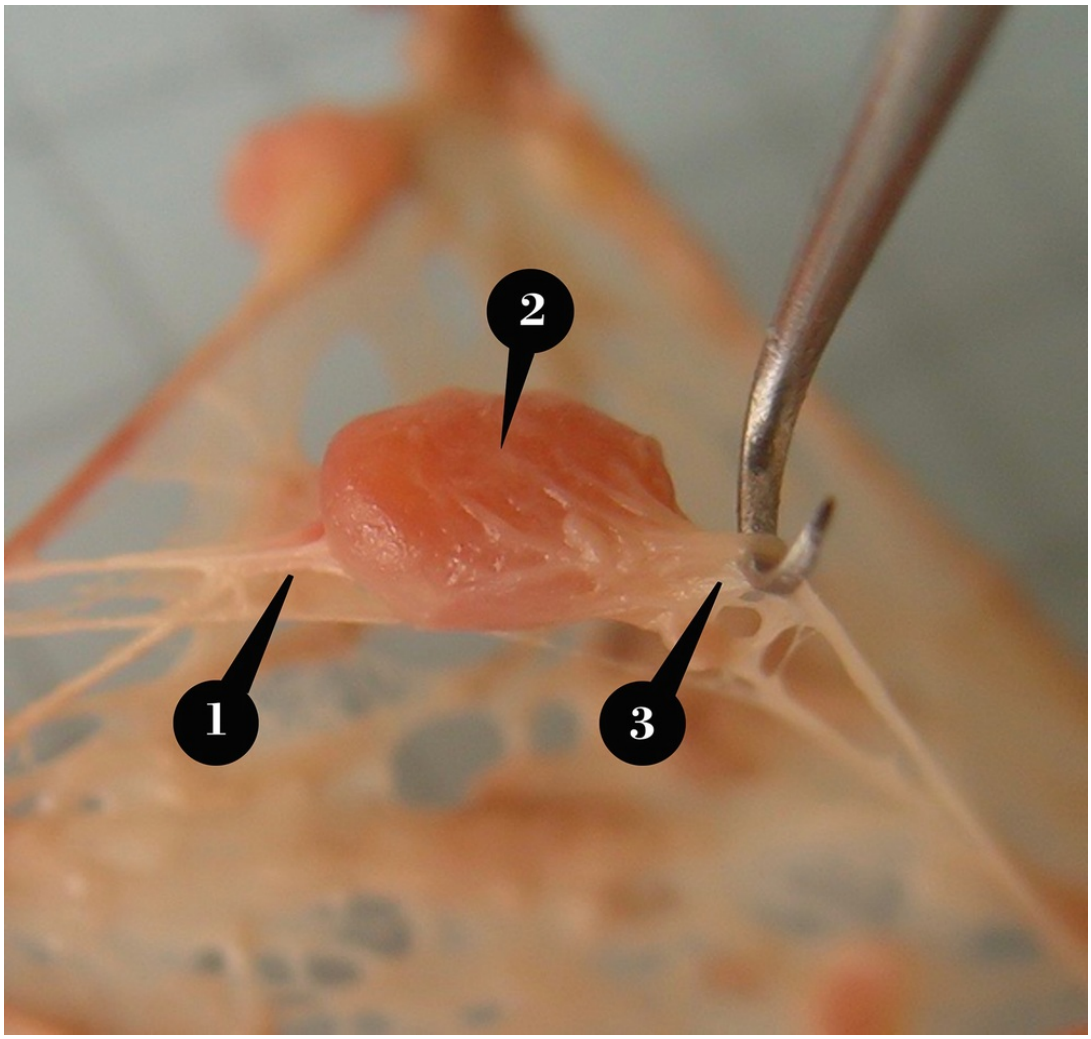


Fig. 5.14 A single postnatal lymph node (2). Figures 1 and 3 – a part of the lymph flow and outflow is represented by newly formed vessels. The node capsule is well-formed

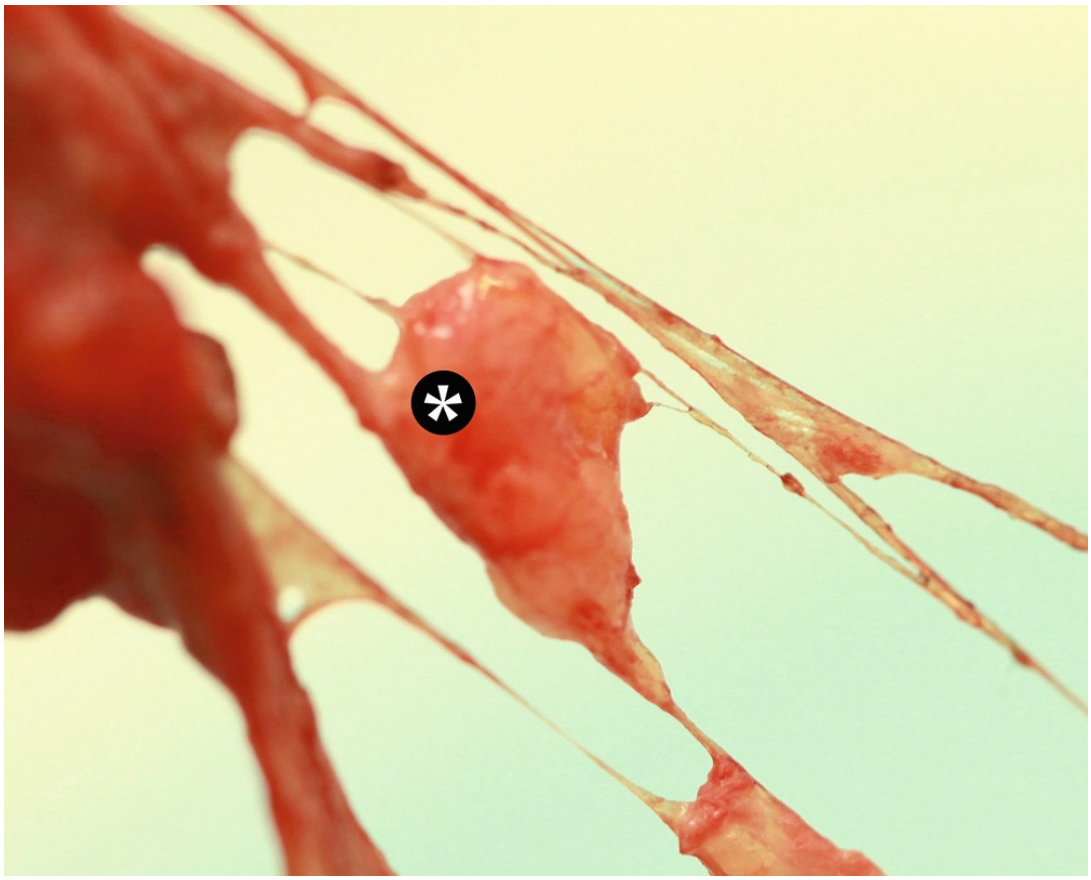


Fig. 5.15 The variant of anatomical organization of the lymph node in breast cancer (∗). The node is located on the formed large vessel. A few extremely thin newly formed vessels are entering to the node. The lymph node capsule is inhomogeneous. The lymph node hilus is not visible

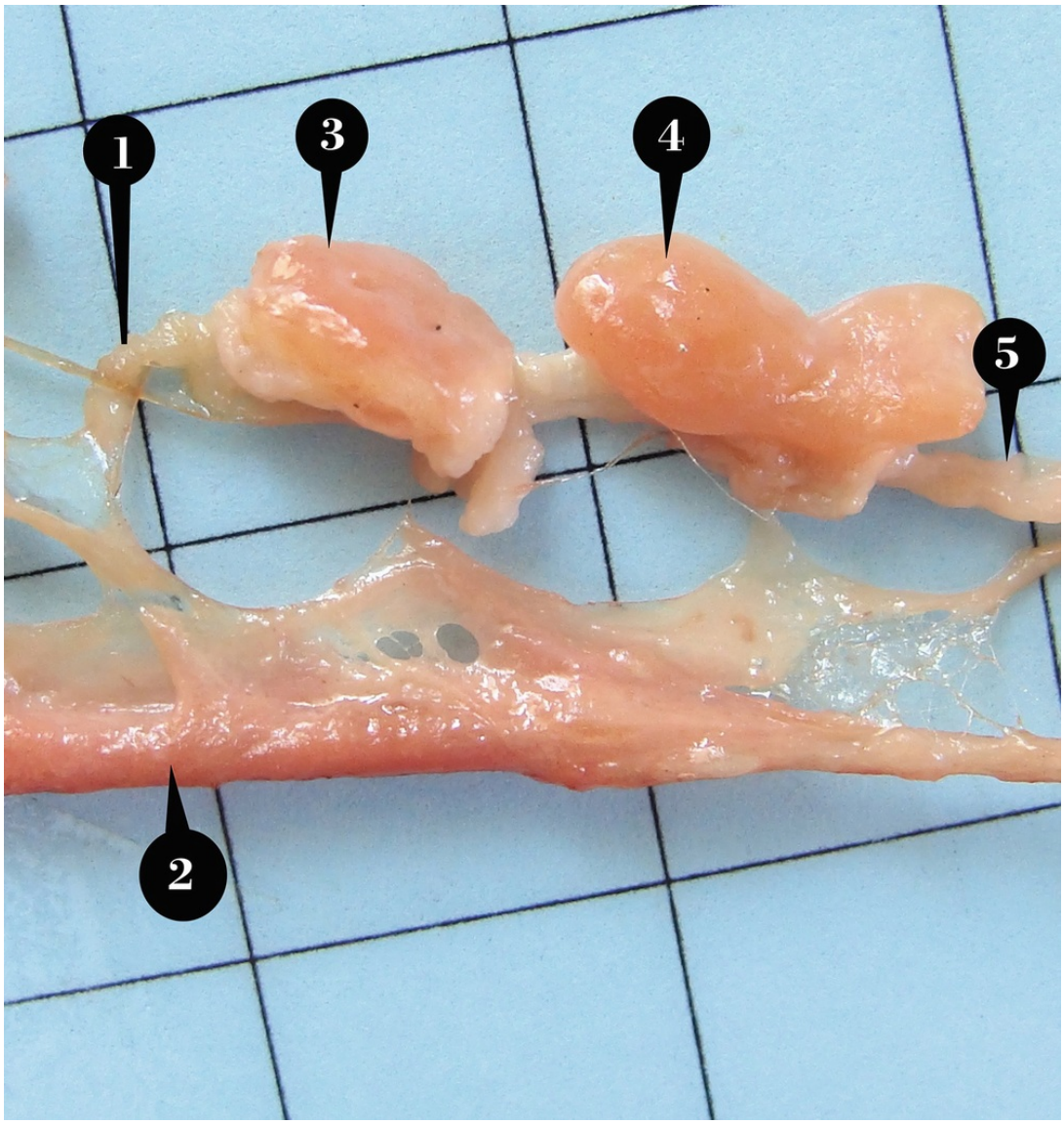


Fig. 5.16 A group of lymph nodes (3 and 4) located on a well-formed lymphatic vessel (1 and 5). The nodes have a close intervascular connection with the great vessel (2) due to newly formed capillaries. The lymph node 3 has a regular shape; its base (the place of connection with the vessel) is extremely pale (avascular zone). The lymph node 4 has an unusual shape; the capsule is without pathological characteristics

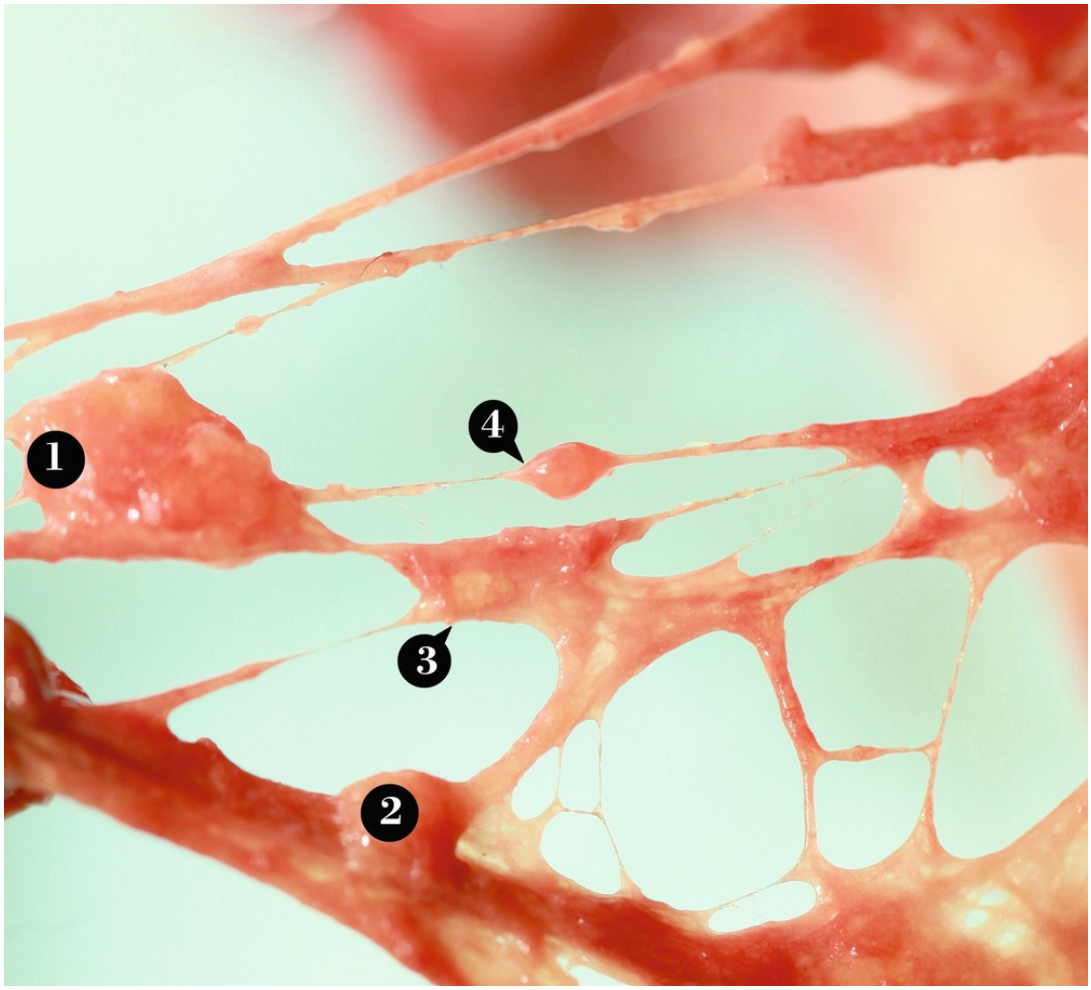


Fig. 5.17 The fragment of lymphatic mapping in breast cancer. Figures 1 and 2 illustrate lymph nodes, and 3 illustrates zone of lymphatic vessels' anastomosing (there are 7 vessels) with the formation of glomeruli and 4 tertiary lymph node (postnatal lymph node) formed within a single vessel and having a simplified structure

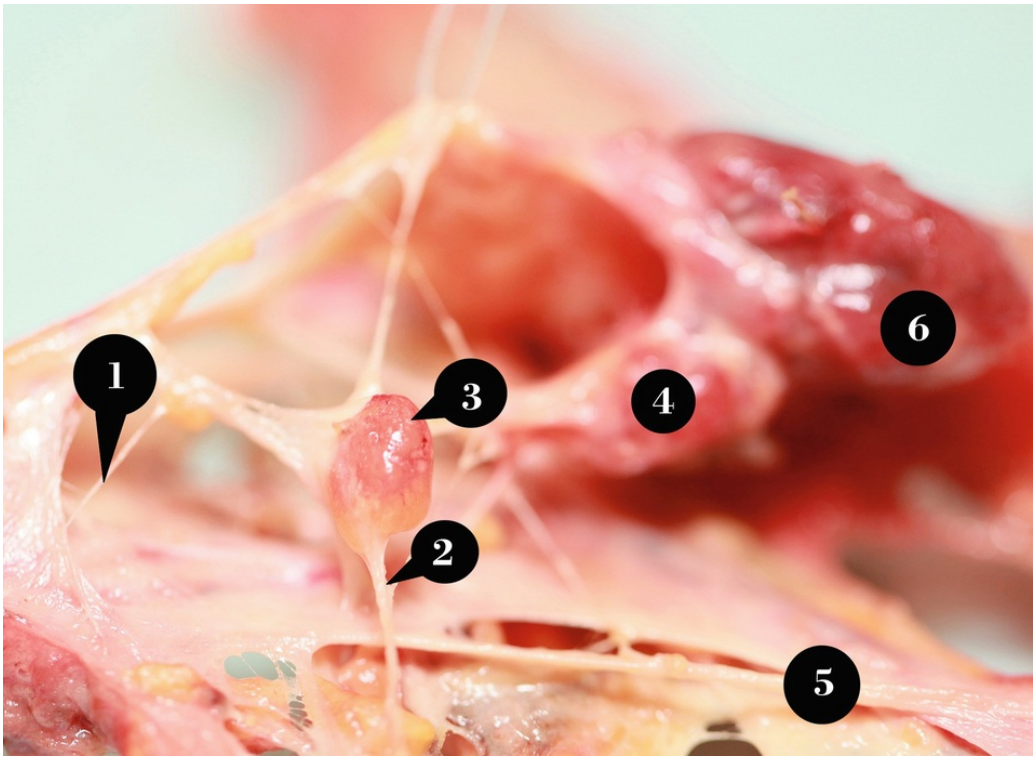


Fig. 5.18 In the foreground, there is a newly formed lymph node (3), 12 mm in size and bean-shaped. In the depth of gross specimen, there are lymph nodes (4,6) affected by metastases (stage III breast cancer). Around the 3 lymph node, there are several (1, 2) newly formed lymphatic vessels. Figure 5 illustrates a transient lymphatic vessel

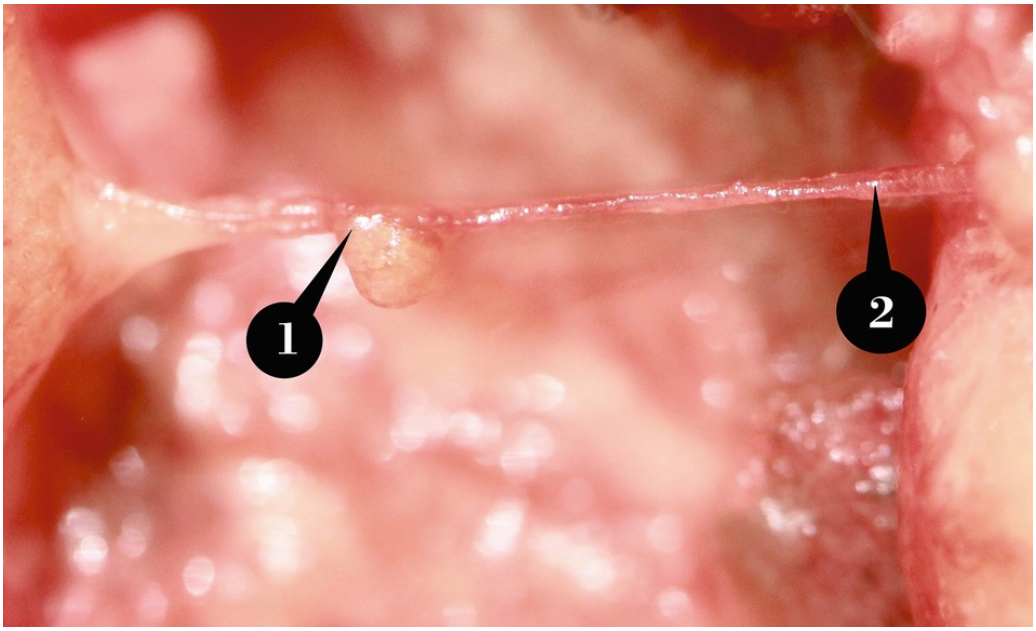


Fig. 5.19 A newly formed lymphatic vessel of small diameter (2) connects two lymph nodes. Figure 1 illustrates a tertiary lymphatic organ which is located on the lymphatic vessel. It is round-shaped, its size is 4 mm, and the capsule contains adipose tissue

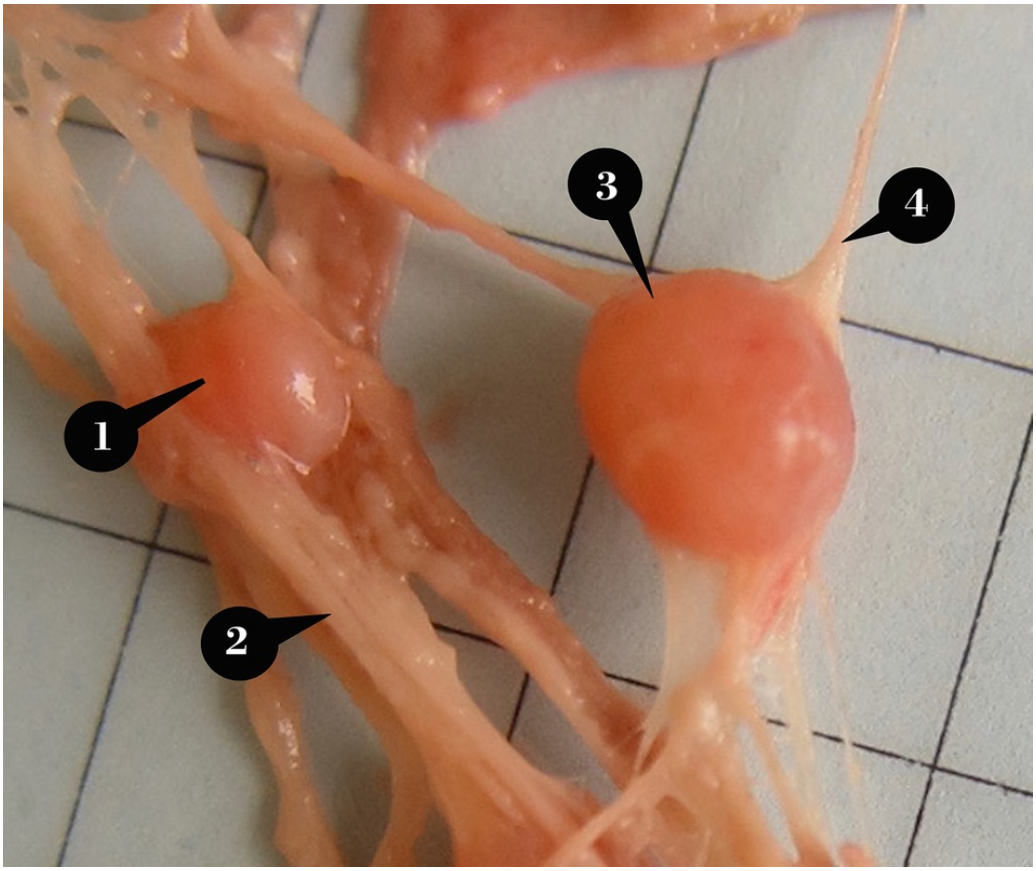


Fig. 5.20 The fragment of lymphatic mapping in breast cancer. There are two globular lymph nodes (1,3), the great vessels (2). The lymph node 3 has a massive capsule; its size is 7 mm. The number of vessels providing perfusion is three

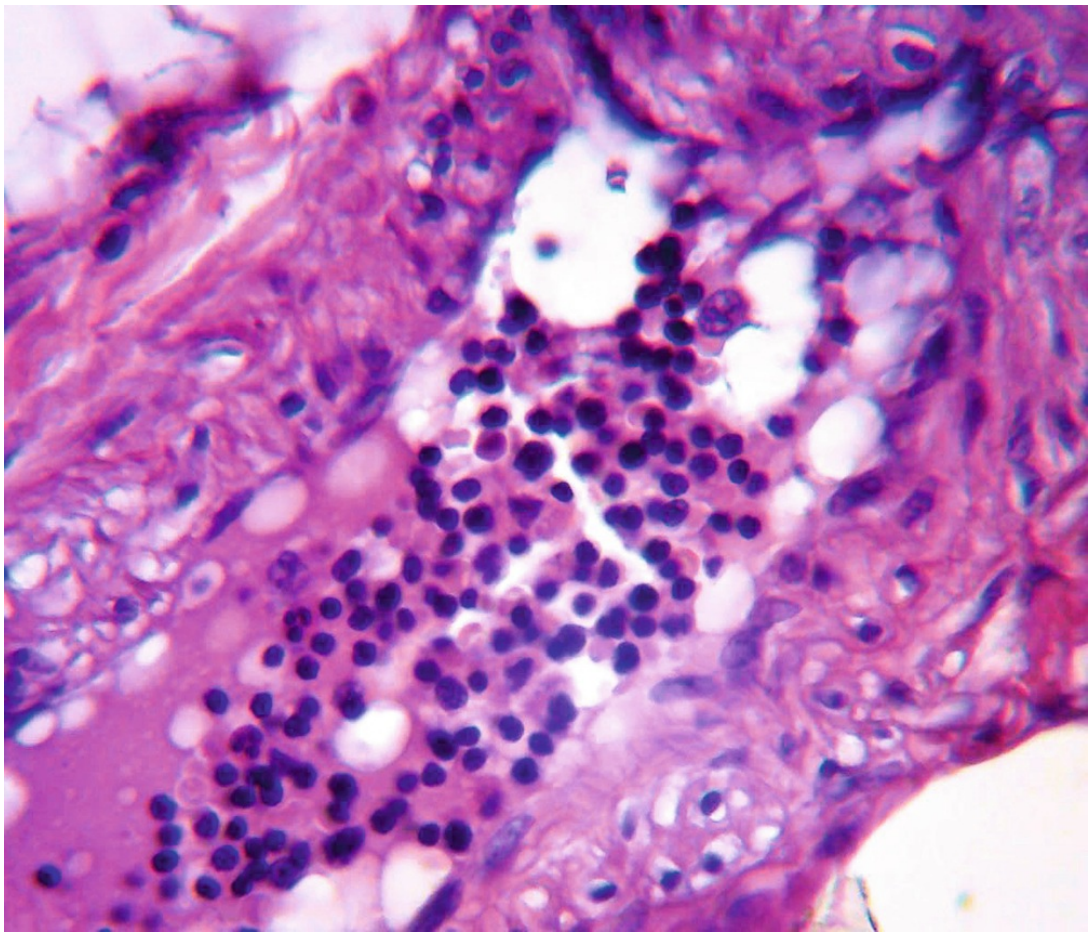


Fig. 5.21 Lymphocyte aggregates in the great lymphatic vessel. Hematoxylin and eosin stain

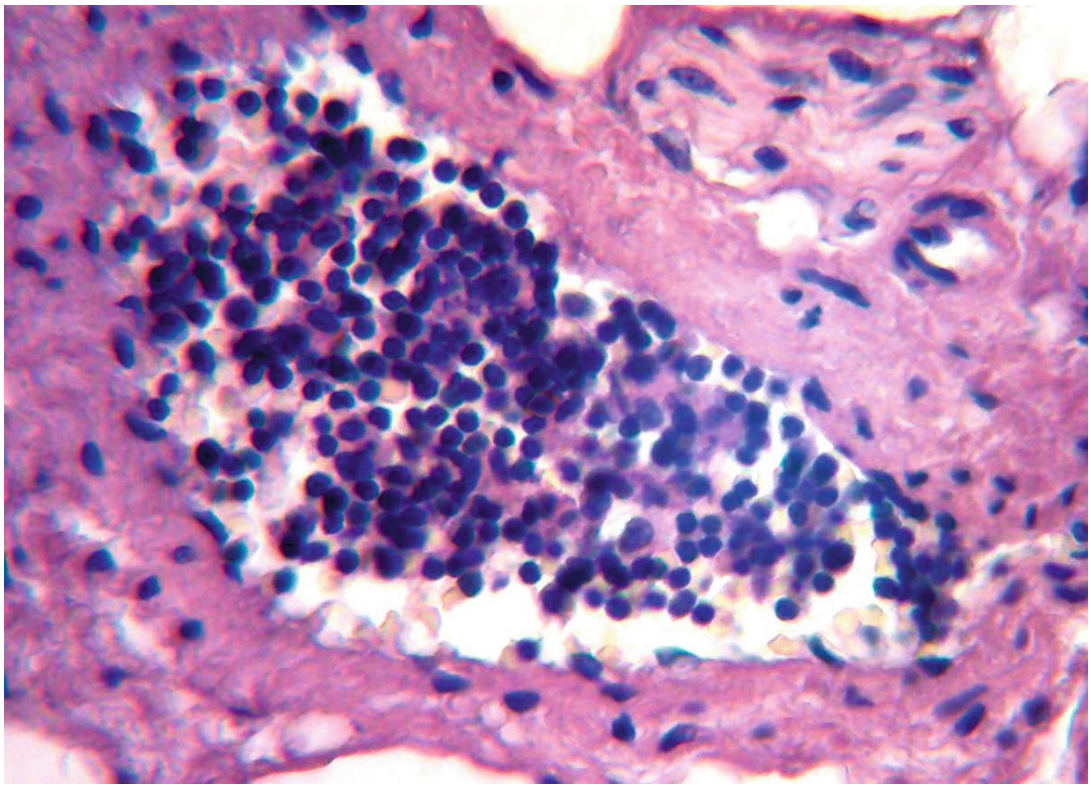
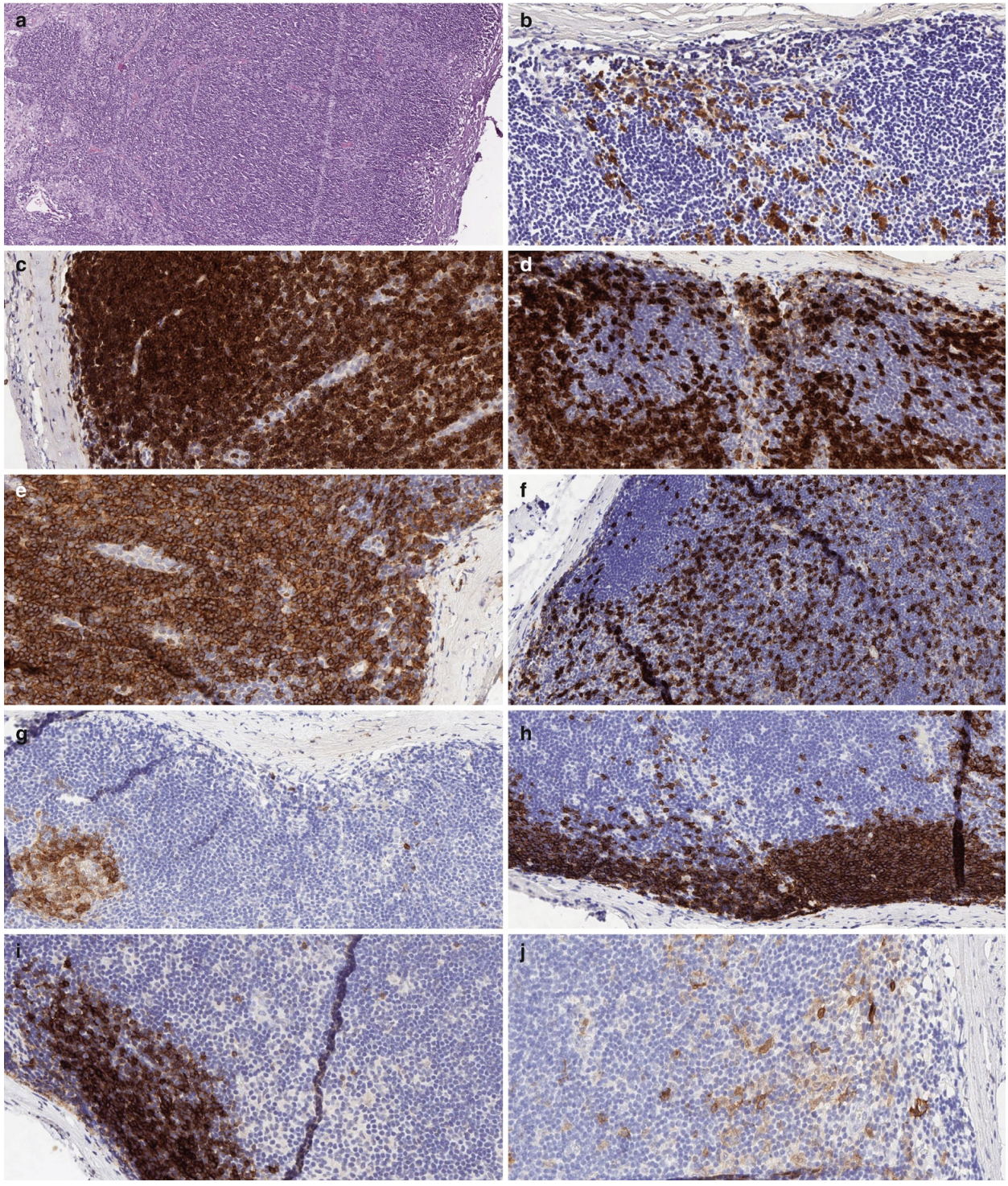


Fig. 5.22 Transverse section of an afferent lymphatic vessel containing lymphocyte aggregates. There are newly formed vessels around the main vascular trunk. Hematoxylin and eosin stain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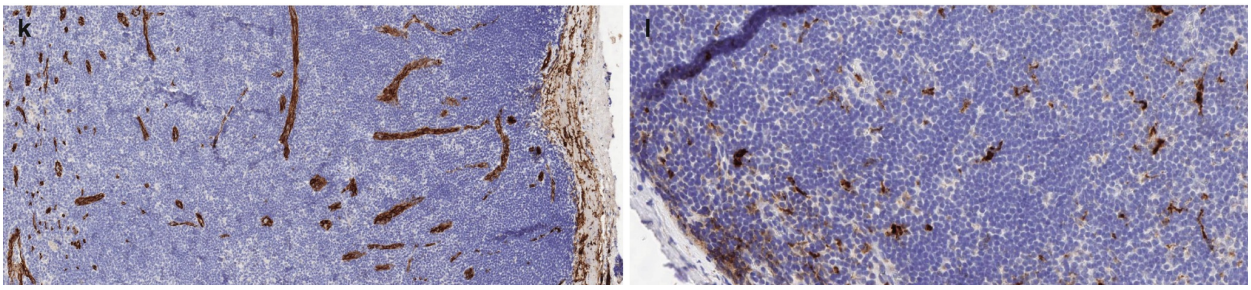
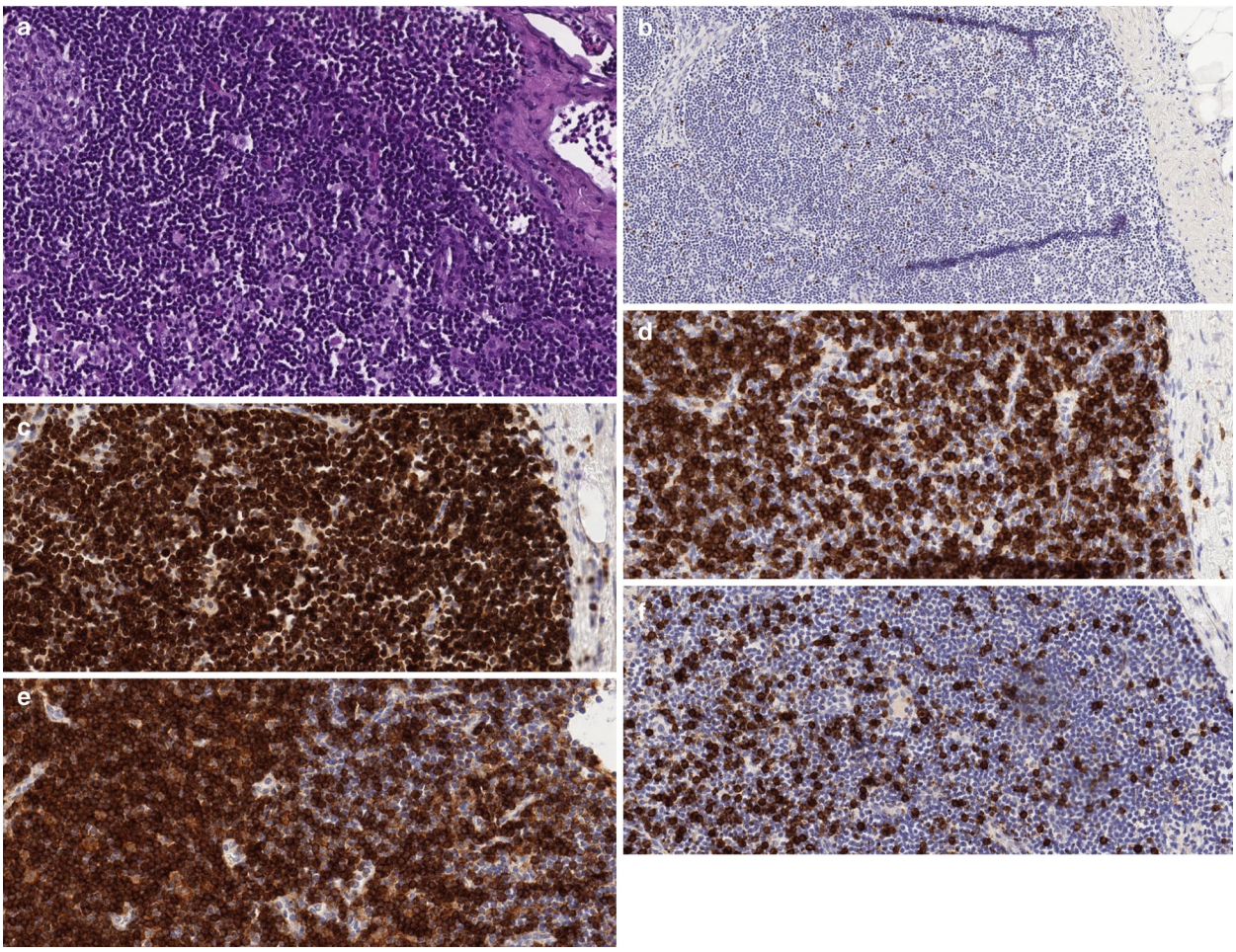


Fig. 5.23 Tertiary lymphatic structures (newly formed lymph node or postnatal lymph node). Lymphoid follicles with germinal centers of different sizes are located mainly in the cortical zone of the lymph node. A marked expansion of paracortex is also noted. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34 (QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain



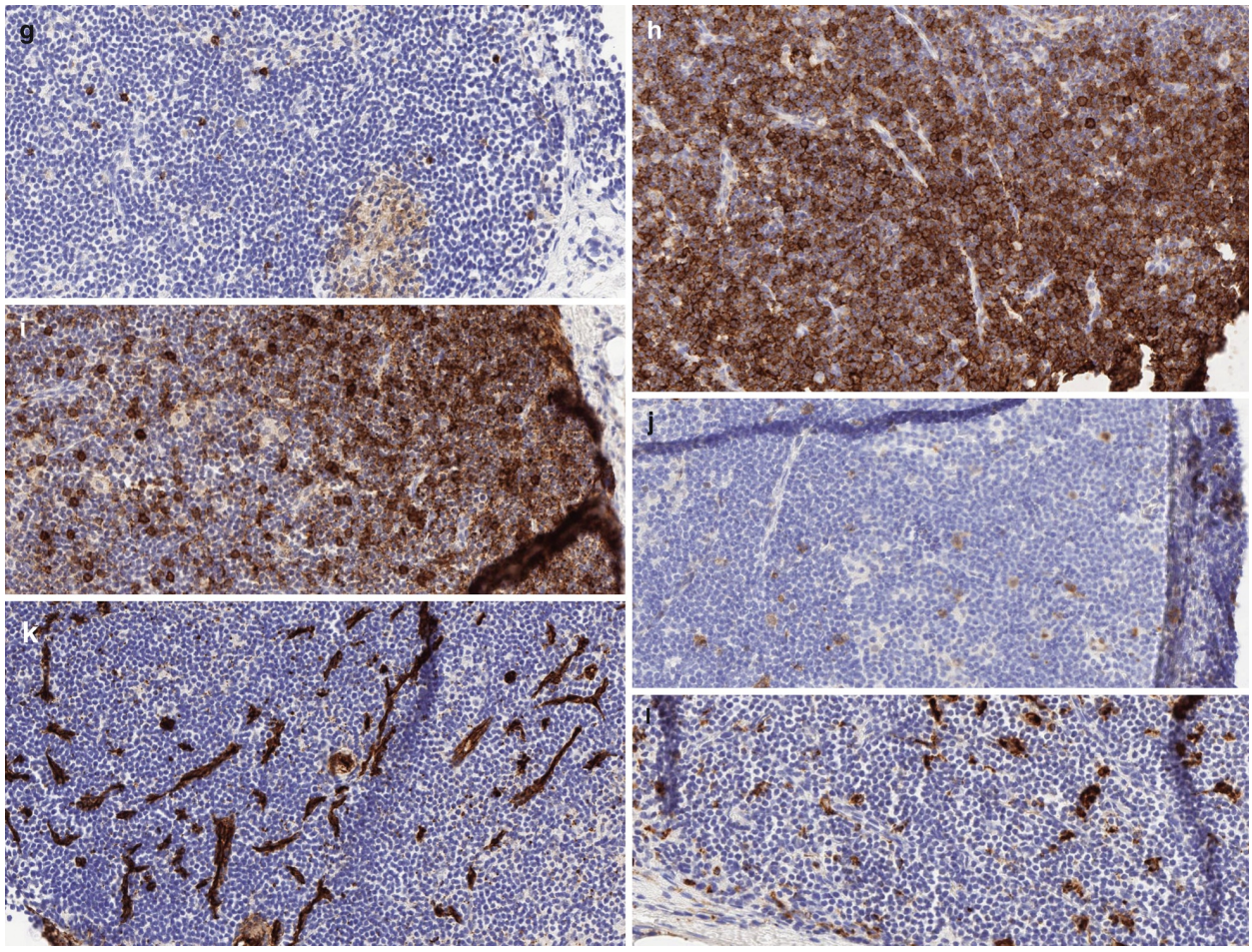


Fig. 5.24 Tertiary lymphatic structures (newly formed lymph node or postnatal lymph node). In all areas of the lymph node are lymphoid follicles with germinal centers of different sizes. (**a**) Hematoxylin and eosin stain, (**b**) anti-S100 (polyclonal) stain, (**c**) anti-Bcl-2 (bcl-2/100/D5) stain, (**d**) anti-CD3 (LN10) stain, (**e**) anti-CD4 (4B12) stain, (**f**) anti-CD8 (4B11) stain, (**g**) anti-CD10 (56C6) stain, (**h**) anti-CD20 (MJ1) stain, (**i**) anti-CD23 (1B12) stain, (**j**) anti-CD30 (1G12) stain, (**k**) anti-CD34 (QBEnd/10) stain, (**l**) anti-CD68 (514H12) stain

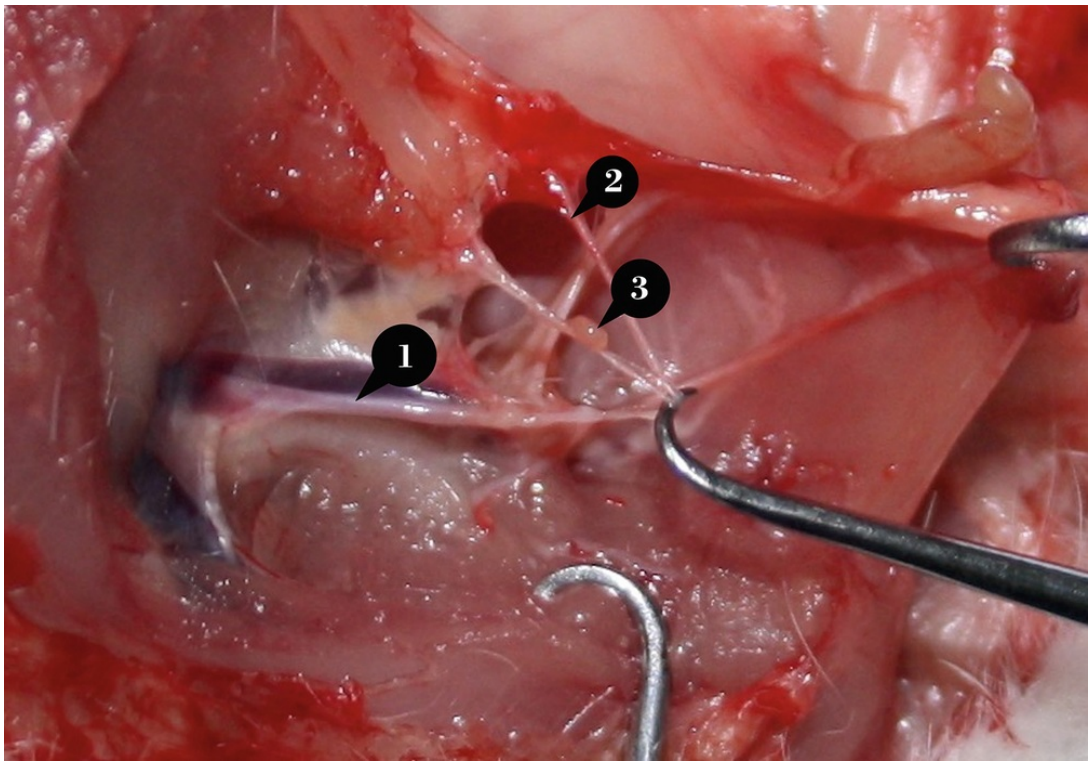


Fig. 5.25 Neolymphogenesis was performed under experimental conditions in a laboratory rodent. Figure 1 illustrates a blood vessel, 2 the newly formed lymph node, and 3 the great lymphatic vessel. Lymphangiogenesis is not active

Conclusion

It is time to summarize the results of the submitted materials and pose a number of questions. First, what is the applied meaning of the results of our multi-year research? In this aspect, there is no doubt that entering the era of personified oncology, we need disease and metastatic process markers, as well as factors of natural antitumor protection. When considering the basic supporting points of personification, we study the primary tumor. At the same time, we understand that this is not enough for today. Therefore, the stage of metastasis and its logistics and histostructural changes in the lymphatic apparatus must become reference points for the personification of treatment and post-hospital rehabilitation. As a side note, nowadays it is commonly used the principle of personified surgical treatment of breast cancer. What does this concept include? It includes priority; it is breast-conserving surgery. Exceptions, in our opinion, can be at atypical breast cancer types and negative factors of prognosis. Oncosurgeons still remember the process of extended lymphatic dissections in many types and locations of breast cancer that were normally performed in advanced cancer and sometimes in early disease. Now these operations are performed much more rare. At the same time, this is the other extreme. It seems to us that lymphatic cancer spread is no less important factor that must be taken into account while extending or narrowing the intensity of lymphatic dissection. A function study of one of the nodes of this collector is extremely insufficient; it is necessary to undertake even more extensive and in-depth studies of this zone. Concerning personified drug therapy of breast cancer, it should be noted that today this issue has reached the highest level of its development, although not universally. But in any cases, the course is chosen to determine specific drug sensitivity of tumor, its safety, in order to

increase treatment response.

Thus, even today we are able to predict clinical course and effect of background drug therapy . However, this is not enough, because many of scientific data obtained in this area contradicts to the real practical life and demands of general work. What does it mean? To date, it is known many delicate stimulation mechanisms of vasculogenesis in cancer, including lymphatic ones. However, if the curative cancer conception provides for angiogenesis inhibition, how should this issue be considered from the point of neo-lymphangiogenesis? The question of the role of tertiary lymphatic organs (newly formed lymph nodes) remains open: what is their role in controlling neoplasia? Questions always remain and they need to be resolved. Practical or applied significance does not end here. We focused only on the main components of this problem.

The second and also important question that the academic community is interested in is as follows: what was new data received that probably contradicted commonly held views and required the collaboration of research centers and institutions?

Summing up this part, we would like to note that the processes of metastasis and wide spread of cancer are very active and rapid, taking place extremely dynamically and very brightly, sequentially absorbing and destroying vital organizational clusters and organs of living biological systems. Many processes of cancer controlling occur in vascular space (which is not always taken into account), lymphoid organs (primary and secondary), and the lymphatic system as a whole.

Turning back to the question of the sentinel lymph node in cancer, it should be noted that this is a notional anatomical and physiological concept. It allows us to understand the dynamics and possible proportion of oncological disease and threat of dissemination. Once again we want to repeat that it would not be correct to consider several nodes as sentinel ones. Why? This

node is the main one, it is like a contractor, and its role in metastasis logistics is very important. At the same time, this node has lymphoid tissue doubles or subcontractors, which also participate in the devitalization of tumor cells and determine the further logistics of cell population. The main or primary sentinel lymph node has a certain resource. And after a certain time, it stops its distribution and antitumor function by delegating it to another node (it can be considered a second-order sentinel lymph node). A number of researchers believe that the sentinel lymph node is the closest one to the tumor. But it is not quite so. Of course, nodes with a high level of neo-lymphangiogenesis may be the primary ones, but this is not always the case. Practically, there are absolutely normal and unmetastasized nodes, but, at the same time, other nodes have signs of secondary tumor lesion. In such cases, it is common to say about “skip” metastases, great metastasis.

Undoubtedly, from our point of view, tumor block of the lymph node and the sentinel lymph node is of substantial significance. The observed cancer tumor thrombi of inflow vessels lead to lumen expansion and failure of the valves, as well as to lymphangia as a whole. The block of sentinel lymph node, failure of valvular apparatus and the large number of newly formed vessels lead to uncontrolled and, what is more, interzonal cancer dissemination . Thus, it is enough to block at least one segment of the sentinel lymph node to change the logistics of lymph movement and so, metastasis takes the form of interzonal character. During our research, we discovered lymphatic vessels transversing to the main vascular bundle, which also evidences a developed interzonal collateral vascular system .

Until now, the metastasis zonality has been considered one of the incommutable laws of metastasis. However, amendments to these laws are necessary, and this, in turn, necessitates the revision of lymphatic dissection problems and cancer staging. It is

important to conduct necessary and detailed morphological examination of the sentinel lymph node , since it is the main node determining cancer prognosis. It can be assumed that if we actively take into account the possibilities of early interzonal metastasis, then cancer staging characteristics by N and M criteria will also be changed.

Important data that we received are also related to the lymph node capsule . It is commonly believed that the capsule retains an unchanged histological structure at all stages of neoplastic process. However, we found that angiogenesis actively proceeds not only in the tumor and lymphatic drainage basin but also in the lymph node capsule itself. We observed a complete replacement of the capsule with capillaries during neoplastic process. In international TNM classification of cancer (2018), accepted worldwide, it is noted that the lymph node capsule is the last one that is involved in neoplastic process, according to centrifugal principle. And this is a very bad prognostic. However, our observations demonstrate that neoplastic process can spread from the capsule to the node depth. That is, the capsule has metastasis, and the lymph node is free of cancer cells continuing to fulfill its biological mission.

Our research has made it possible to elicit new facts that have not been previously described in general publications. They relate primarily to the development of tertiary lymphoid organs. Newly formed lymph vessels have not been discussed for a long time, because this is an obvious fact, but the development of new lymph nodes causes a great controversy. We discovered these nodes and described them later in authoritative scientific publications (Biomedicine & Pharmacotherapy, 2013, Vol. 67.-№5.-P.363-366; Biomedicine –Pharmacotherapy, 2013, №5.-Vol.67.-P.637-642). We presented these materials to a wide range of scientists who recognized the possibility of neolymphogenesis phenomenon in cancer. We would like to express our gratitude to the following

scientists for their support of this project and recommendations for further implementation of scientific outlook: academicians of the Russian Academy of Sciences Mikhail Davydov, Yuriy Borodin, Vladimir Anisin, and Mikhail Dubina (Russia), Professors Kazuo Umezawa (Japan), Ivars Kalvinsh (Latvia), Gerhard Schaller (Germany), Rediger Horsmann (Germany), etc.

In conclusion of this scientific publication, we would like to address one more issue. Our scientific body carries out a great innovative work supported by the Skolkovo Innovation Center, and a number of studies are funded by this Center. It should be noted that the application was carried over for consideration of a very authoritative international expert group which found these studies promising and most importantly realizable. The project concept concerns the development of a new approach to personified cancer biotherapy (patent for invention N2526160, registered on June 25, 2011), namely, starting a forming process of tertiary lymphadenoid structures (neolymphogenesis) in a biological system that is deprived of this possibility due to various circumstances. At present, we are conducting a very important part of research, namely, the search for a key protein that develops the mechanism of neolymphogenesis. We believe that in our subsequent publications, we will be able to demonstrate these results.

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